






# Oral Nutritional Supplement Prescription and Patient-Reported Symptom Burden Among Patients With Late-Stage Non-Dialysis Chronic Kidney Disease

Canadian Journal of Kidney Health and Disease  
Volume 11: 1–8  
© The Author(s) 2024  
Article reuse guidelines:  
sagepub.com/journals-permissions  
DOI: 10.1177/20543581241228731  
journals.sagepub.com/home/cjk



Michelle M. Y. Wong<sup>1,2</sup>, Yuyan Zheng<sup>2</sup>, Bingyue Zhu<sup>2</sup>,  
Lee Er<sup>2</sup>, Mohammad Atiquzzaman<sup>2</sup>, Alexandra Romann<sup>2</sup>,  
Dani Renouf<sup>3</sup>, Zainab Sheriff<sup>1,2</sup>, and Adeera Levin<sup>1,2,3</sup>

## Abstract

**Background:** Malnutrition and protein-energy wasting (PEW) are nutritional complications of advanced chronic kidney disease (CKD) that contribute to morbidity, mortality, and decreased quality of life. No previous studies have assessed the effect of oral nutritional supplements (ONSs) on patient-reported symptom burden among patients with non-dialysis CKD (CKD-ND) who have or are at risk of malnutrition/PEW.

**Objective:** The objective of this study was (1) to quantify the associations between baseline nutritional parameters and patient-reported symptom scores for wellbeing, tiredness, nausea, and appetite and (2) to compare the change in symptom scores among patients prescribed ONS with patients who did not receive ONS in a propensity-score–matched analysis.

**Design:** This study conducted observational cohort analysis using provincial registry data.

**Setting:** This study was done in multidisciplinary CKD clinics in British Columbia.

**Patients:** Adult patients >18 years of age with CKD-ND entering multidisciplinary CKD clinics between January 1, 2010–July 31, 2019 who had at least 2 Edmonton Symptom Assessment System Revised: Renal (ESASr:Renal) assessments.

**Measurements:** The measurements include nutrition-related parameters such as body mass index (BMI), serum albumin, serum phosphate, serum bicarbonate, neutrophil-to-lymphocyte ratio (NLR), and ESASr:Renal scores (overall and subscores for wellbeing, tiredness, nausea, and appetite).

**Methods:** Multivariable linear regression was applied to assess associations between nutritional parameters and ESASr:Renal scores. Propensity-score matching using the greedy method was used to match patients prescribed ONS with those not prescribed ONS using multiple demographic, comorbidity, health care utilization, and temporal factors. Linear regression was used to assess the association between first ONS prescription and change in ESASr:Renal overall score and subscores for wellbeing, tiredness, nausea, and appetite.

**Results:** Of total, 2076 patients were included. Higher baseline serum albumin was associated with lower overall ESASr:Renal score (−0.20, 95% confidence interval [CI] = −0.40 to −0.01 per 1 g/L increase in albumin), lower subscores for tiredness (−0.04, 95% CI = −0.07 to −0.01), nausea (−0.03, 95% CI = −0.04 to −0.01), and appetite (−0.03, 95% CI = −0.06 to −0.01). Higher BMI was associated with higher overall ESASr:Renal score (0.32, 95% CI = 0.16 to 0.48 per 1 kg/m<sup>2</sup> increase in BMI), higher symptom subscores for wellbeing (0.02, 95% CI = 0.00 to 0.04) and tiredness (0.05, 95% CI = 0.02 to 0.07). Higher baseline NLR was associated with higher overall score (0.21, 95% CI = 0.03 to 0.39 per 1 unit increase in NLR), higher symptom subscores for wellbeing (0.03, 95% CI = 0.01 to 0.05) and nausea (0.03, 95% CI = 0.02 to 0.05). In the propensity-score–matched analysis, there were no statistically significant associations between ONS prescription and change in overall

<sup>1</sup>Division of Nephrology, Department of Medicine, The University of British Columbia, Vancouver, BC, Canada

<sup>2</sup>BC Renal, Vancouver, BC, Canada

<sup>3</sup>St. Paul's Hospital, Providence Health Care, Vancouver, BC, Canada

## Corresponding Author:

Michelle M. Y. Wong, Division of Nephrology, Department of Medicine, The University of British Columbia, 1081 Burrard Street, Vancouver, BC V6Z 1Y6, Canada.

Email: mimywong@mail.ubc.ca



ESASr:Renal (beta coefficient for change in ESASr:Renal = 0.17, 95% CI = -2.64 to 2.99) or for subscores for appetite, tiredness, nausea, and wellbeing.

**Limitations:** Possible residual confounding. The ESASr:Renal assessments were obtained routinely only in patients with G5 CKD-ND and/or experiencing significant CKD-related symptoms.

**Conclusions:** This exploratory observational analysis of patients with advanced non-dialysis CKD demonstrated BMI, serum albumin, and NLR were modestly associated with patient-reported symptoms, but we did not observe an association between ONS use and change in ESASr:Renal scores.

## Abrege

**Contexte:** La malnutrition et la dénutrition protéino-énergétique (DPÉ) sont des complications nutritionnelles de l'insuffisance rénale chronique (IRC) de stade avancé qui contribuent à la morbidité, à la mortalité et à la diminution de la qualité de vie associées à la maladie. Aucune étude n'a évalué l'effet des suppléments nutritionnels administrés par voie orale (SNO) sur le fardeau des symptômes autodéclarés par les patients non dialysés atteints d'IRC (IRC-ND) et souffrant de malnutrition/DPÉ ou risquant d'en souffrir.

**Objectifs:** (1) Quantifier les associations entre les paramètres nutritionnels initiaux et les scores des symptômes autodéclarés en lien avec le bien-être, la fatigue, les nausées et l'appétit. (2) Comparer, dans une analyse des scores de propension appariés, la variation des scores associés aux symptômes des patients ayant reçu une ordonnance de SNO par rapport aux patients n'en ayant pas reçu.

**Conception:** Analyse de cohorte observationnelle à partir des données du registre provincial.

**Cadre:** Cliniques multidisciplinaires d'IRC en Colombie-Britannique.

**Sujets:** Des patients adultes atteints d'IRC-ND admis entre le 1<sup>er</sup> janvier 2010 et le 31 juillet 2019 dans des cliniques multidisciplinaires d'IRC avec au moins deux évaluations selon l'Échelle d'évaluation Edmonton pour l'insuffisance rénale (ESASr:renal—Edmonton Symptom Assessment System Revised: Renal).

**Mesures:** Les paramètres liés à la nutrition: indice de masse corporelle (IMC), albumine sérique, phosphate sérique, bicarbonate sérique, rapport neutrophiles/lymphocytes (RNL), ainsi que les scores ESASr:renal (scores globaux et scores secondaires pour le bien-être, la fatigue, les nausées et l'appétit).

**Méthodologie:** La régression linéaire multivariable a servi à évaluer les associations entre les paramètres nutritionnels et les scores ESASr:renal. Une correspondance des scores de propension par la méthode Greedy a été utilisée pour appairer des patients ayant reçu ordonnance de SNO avec des patients n'en ayant pas reçu selon plusieurs facteurs démographiques, les comorbidités, l'utilisation des soins de santé et des facteurs temporels. La régression linéaire a servi à évaluer l'association entre la première ordonnance de SNO et la variation des scores globaux et des scores secondaires de l'ESASr:renal pour le bien-être, la fatigue, les nausées et l'appétit.

**Résultats:** Au total, 2 076 patients ont été inclus à l'étude. Un taux d'albumine sérique plus élevé à l'inclusion était associé à un score ESASr:renal global plus faible (-0,20 [IC 95 %: -0,40 à -0,01 pour 1 g/L d'augmentation de l'albumine]) et à des scores secondaires plus faibles pour la fatigue (-0,04 [IC 95 %: -0,07 à -0,01]), les nausées (-0,03 [IC 95 %: -0,04 à 0,01]) et l'appétit (0,03 [IC 95 %: -0,06 à -0,01]). Un IMC plus élevé était associé à un score ESASr:renal global plus élevé (0,32 [IC 95 %: 0,16 à 0,48 par augmentation de 1 kg/m<sup>2</sup> de l'IMC]), des scores secondaires de symptômes plus élevés pour le bien-être (0,02 [IC 95 %: 0,00 à 0,04]) et la fatigue (0,05 [IC 95 %: 0,02 à 0,07]). Un RNL initial plus élevé était associé à un score ESASr:renal global plus élevé (0,21 [IC 95 %: 0,03 à 0,39 par unité d'augmentation du RNL]), des scores secondaires de symptômes plus élevés pour le bien-être (0,03 [IC 95 %: 0,01 à 0,05]) et les nausées (0,03 [IC 95 %: 0,02 à 0,05]). Dans l'analyse des scores de propension appariés, aucune association statistiquement significative n'a été observée entre une ordonnance de SNO et une variation significative dans les scores globaux de l'ESASr:renal (coefficient bêta de variation de l'ESASr:renal: 0,17 [IC 95 %: -2,64 — à 2,99]) ou les scores secondaires pour l'appétit, la fatigue, les nausées et le bien-être.

**Limites:** Possibilité de facteurs de confusion résiduels. Les évaluations ESASr:renal ont été effectuées de routine uniquement pour les patients atteints d'IRC-ND G5 et/ou présentant des symptômes importants liés à l'IRC.

**Conclusion:** Cette analyse observationnelle exploratoire portant sur des patients atteints d'IRC avancée non dialysés a démontré que l'IMC, l'albumine sérique et le RNL étaient associés de façon modeste aux symptômes autodéclarés. Toutefois, aucune association n'a été observée entre une ordonnance de SNO et une variation des scores ESASr:renal.

## Keywords

malnutrition, protein-energy wasting, oral nutritional supplement, symptom burden, chronic kidney disease, patient-reported outcomes

## Introduction

Malnutrition and protein-energy wasting (PEW) are nutritional complications of advanced chronic kidney disease (CKD) that contribute to morbidity, mortality, and decreased quality of life.<sup>1,2</sup> Among patients with non-dialysis CKD (CKD-ND), the prevalence of PEW is 11% to 54%.<sup>3</sup> Following nutritional counseling, treatment with oral nutritional supplements (ONSs) is recommended by renal nutrition guidelines for management of malnutrition/PEW.<sup>4</sup>

We previously demonstrated in an observational study that ONS prescription was associated with improvements in nutritional parameter slopes among patients with CKD-ND who were at risk of malnutrition/PEW in British Columbia,<sup>5,6</sup> which has a province-wide, government-funded ONS policy stewarded by dietitians.<sup>7</sup> Although a few previous studies of ONS therapy have assessed quality-of-life domains among patients receiving hemodialysis (HD),<sup>8-10</sup> there are no studies assessing the effect of ONS on patient-reported symptom burden among patients with CKD-ND who have or are at risk of malnutrition/PEW.

Therefore, we performed an observational study utilizing registry data for patients with CKD-ND in BC, with the following aims: (1) to quantify the associations between baseline nutritional parameters and symptom scores for wellbeing, tiredness, nausea, appetite, in an exploratory analysis and (2) to compare the change in symptom scores among patients prescribed ONS with patients who did not receive any ONS prescription, using a propensity-score-matched analysis.

## Materials and Methods

This cohort analysis included adult patients >18 years of age with CKD-ND who entered multidisciplinary CKD clinics in BC between January 1, 2010 and July 31, 2019, and who had at least 2 Edmonton Symptom Assessment System Revised: Renal (ESASr:Renal) assessments done. For patients prescribed ONS, at least 1 ESASr:Renal assessment before ONS initiation and at least 1 ESASr:Renal assessment after ONS initiation were required. For non-ONS users, they were required to have at least 2 ESASr:Renal assessments done 0.5 to 24 months apart. Data were extracted from the Patient Records and Outcome Management Information System, an electronic registry of kidney patients in BC. Patients with previous renal transplant were excluded from the analysis. Ethics approval was obtained from the University of British Columbia-Providence Health Care Institute (study number: H19-01154).

British Columbia has a provincial Nutritional Supplement Policy<sup>7</sup> that provides ONS free of charge for patients in whom any of the following conditions occur and cannot be addressed through nutritional counseling alone: unintentional weight loss >10% of usual body weight in the past 6 months, current weight <90% of desirable body weight, nutrient intake <80% recommended, and/or current

hypercatabolic state. Oral nutritional supplement available under this policy (Supplemental Table 1) include general ONS, renal-specific ONS, diabetes-specific ONS, and protein-only ONS. Renal dietitians determine the ONS prescription based on the patient's nutritional status, dietary intake, caloric/protein needs, comorbidities, medical status, and patient preference. Duration of ONS treatment is variable and based on regular evaluation by a renal dietitian.

British Columbia has a province-wide Systematic Symptom Assessment and Management policy that utilizes ESASr:Renal to assess symptom burden of patients followed at multidisciplinary CKD clinics who meet the following criteria: eGFR <15 mL/min/1.73 m<sup>2</sup>, and/or reporting significant CKD-related symptoms.<sup>11</sup> ESASr:Renal encompasses 12 symptoms: pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, wellbeing, shortness of breath, pruritus, sleeping problems, and restless legs. Patients can also add and rate a 13th symptom that is not already listed. For each symptom, patients are asked to rate their experience over the past week using a scale of 0 to 10 (0 = no symptom, 10 = severe). Patients complete their own ESAS, but if they cannot independently perform this task, it is completed with the assistance of a caregiver. The ESAS can also be administered by a Kidney Care Clinic team member by telemedicine if the patient is not attending clinic in person.

Any ESASr:Renal subscore of symptom that was left unanswered by the patients was assumed to be no symptom with a score of "0." Sensitivity analyses were performed by excluding patients with unanswered subcomponent values to validate the assumption. Missing data were observed in some nutritional parameters of interest; for example, 34.2% missingness in body mass index (BMI) and 18.3% in urine albumin-to-creatinine ratio (ACR). We assumed data were missing at random and generated 20 imputed data sets based on multivariate imputation by chained equations (MICE). All 13 baseline and post-ONS ESASr:Renal subscores, nutritional parameters of interest, and patients' baseline characteristics were included in the imputation model.

Using baseline data within 6 months of entry to the CKD clinic, multivariable linear regression was applied to assess associations between nutritional parameters (BMI, serum albumin, serum phosphate, serum bicarbonate, NLR) and ESASr:Renal scores (overall and subscores for wellbeing, tiredness, nausea, and appetite) within each imputed data set. We selected these 4 ESASr:Renal subscores because we hypothesized they may be linked with nutritional status. The models were adjusted for age, sex, health region, estimated glomerular filtration rate (eGFR), urine ACR, cause of CKD, hypertension, diabetes, any cardiovascular disease, parathyroid hormone (PTH), ferritin, iron saturation, and hemoglobin. Estimated effects of the covariates and confidence intervals were pooled via Rubin's rules from each imputed data set.<sup>12</sup>

Propensity-score matching using the greedy method<sup>13-15</sup> was used to match patients prescribed ONS with those not

**Table 1.** Baseline Patient Characteristics After Multiple Imputation.

	Original cohort		Matched cohort	
	Patients who received $\geq 1$ ONS prescription (N = 434)	Patients who did not receive ONS prescription (N = 2326)	Patients who received $\geq 1$ ONS prescription (407 $\leq$ N $\leq$ 427)	Patients who did not receive ONS prescription (407 $\leq$ N $\leq$ 427)
Age (y)	74.1 (65.7-80.8)	71.0 (61.8-78.7)	74.1 (65.4-80.7)	72.5 (63.8-79.9)
Female (%)	171 (39.4%)	904 (38.9%)	39.7%	41.26%
Comorbidities (%)				
Diabetes	232 (53.5%)	1381 (59.4%)	54.0%	53.9%
Hypertension	362 (83.4%)	2039 (87.7%)	83.5%	83.4%
Any cardiovascular disease	212 (48.9%)	976 (42.0%)	48.6%	48.7%
Estimated glomerular filtration rate (mL/min/1.73 m <sup>2</sup> )	18.0 (13.0-25.0)	24.0 (17.0-30.8)	18.5 (13.0-25.0)	19.4 (14.1-24.7)
Urine ACR (mg/mmol)	48.1 (9.1-174.3)	35.2 (6.3-141.0)	47.5 (8.9-174.6)	48.9 (9.3-160.7)
Body mass index (kg/m <sup>2</sup> )	24.8 (22.3-28.6)	28.2 (24.7-32.5)	24.8 (22.4-28.7)	25.5 (23.0-28.8)
Serum albumin (g/L)	39.0 (35.0-42.0)	40.0 (38.0-43.0)	39.0 (35.5-42.0)	39.0 (36.0-41.5)
Serum phosphate (mmol/L)	1.3 (1.1-1.5)	1.2 (1.1-1.4)	1.3 (1.1-1.5)	1.3 (1.1-1.5)
Serum bicarbonate (mmol/L)	24.0 (21.0-26.0)	25.0 (22.1-27.0)	24.0 (21.0-26.0)	24.0 (21.6-26.1)
Serum ferritin ( $\mu$ g/L)	160.5 (84.2-277.3)	126.4 (64.3-235.7)	157.8 (82.7-273.3)	143.7 (69.1-283.0)
Iron % saturation	22 (17-30)	24 (18-31)	22 (17-30)	23 (17-19)
Hemoglobin (g/L)	108.0 (99.0-117.0)	117.0 (106.0-128.4)	108.0 (99.6-117.8)	108.2 (97.5-118.8)
Parathyroid hormone (pmol/L)	13.8 (8.1-23.6)	11.4 (7.1-17.9)	13.6 (8.1-22.9)	13.7 (8.2-22.3)
Neutrophil-to-lymphocyte ratio	3.4 (2.5-5.2)	2.9 (2.1-4.1)	3.4 (2.5-5.1)	3.2 (2.3-4.6)
Number of medications during covariate assessment period	11 (8-15)	10 (7-13)	11 (8-15)	11.4 (8.2-15.0)
Time between ESASr:Renal assessments (days)	126 (84-201)	166 (91-231)	126.4 (84.0-202.6)	127.7 (75.9-193.8)

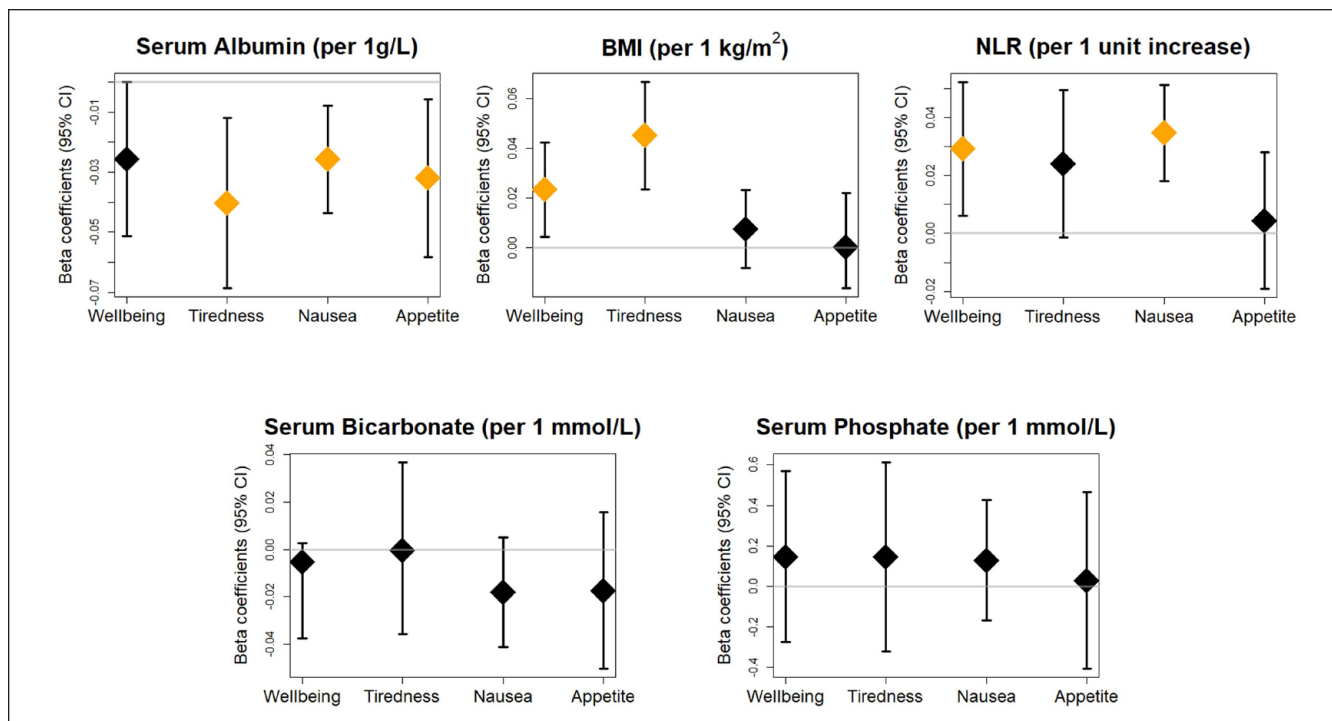
Note. Number (percentage) or median (averages of IQR from each imputed data set) are reported. ACR = albumin-to-creatinine ratio; ESASr:Renal = Edmonton Symptom Assessment System Revised: Renal; ONS = oral nutritional supplement.

prescribed ONS using covariate assessment period of 12 months prior to first ONS prescription within each imputed data set. The propensity score included age, sex, eGFR, urine ACR, hypertension, diabetes, other cardiovascular disease comorbidities, BMI, serum albumin, serum phosphate, serum bicarbonate, serum PTH, iron saturation, serum ferritin, hemoglobin, NLR, health authority, date of entry to CKD clinic, time between ESASr:Renal measurements, and number of medications prescribed during the covariate assessment period. Laboratory data from the closest date to first ONS prescription were used for patients prescribed ONS. For non-ONS users, data from the date closest to the first ESASr:Renal assessment were used. The primary outcome was change in overall ESASr:Renal score, and secondary outcomes included change in ESASr:Renal subscores for wellbeing, tiredness, nausea, and appetite. For ONS users, change in ESASr:Renal was defined as the difference between the first available ESASr:Renal scores post-ONS vs

baseline ESASr:Renal during covariate assessment period, and for non-ONS users, the change in ESASr:Renal was the difference between 2 consecutive ESASr:Renal scores assessed 0.5 to 24 months apart. Linear regression was used to assess the association between first ONS prescription and change in ESASr:Renal scores within each imputed data set. A pooled estimated average marginal treatment effect of ONS prescription was calculated using Rubin's rule. All analyses were performed using SAS version 9.4 (SAS Institute, Inc, Cary, North Carolina).

## Results

A total of 2076 patients with CKD-ND were included in the analysis (Supplemental Figure 1). Patients prescribed ONS were older, had lower eGFR, hemoglobin and serum albumin, and greater serum PTH compared with those not prescribed ONS (Table 1). Oral nutritional supplement users



**Figure 1.** Associations between baseline nutritional parameters and patient-reported symptom burden among patients with non-dialysis CKD.

Note. Statistically significant associations ( $p < 0.05$ ) are in orange. BMI = body mass index; CI = confidence interval; CKD = chronic kidney disease; NLR = neutrophil-to-lymphocyte ratio.

had higher baseline overall ESASr:Renal scores (median = 32.5, interquartile range [IQR] = 18-51), compared with non-users (23, IQR = 10-39), as well as higher subscores for tiredness, appetite, and wellbeing (Supplemental Table 2).

Higher baseline serum albumin was associated with lower overall ESASr:Renal score ( $-0.20$ , 95% CI =  $-0.40$  to  $-0.01$  per 1 g/L increase in albumin), lower tiredness subscore ( $-0.04$ , 95% CI =  $-0.07$  to  $-0.01$ ), lower nausea subscore ( $-0.03$ , 95% CI =  $-0.04$  to  $-0.01$ ), and lower appetite subscore ( $-0.03$ , 95% CI =  $-0.06$  to  $-0.01$ ) (Figure 1). Higher BMI was associated with higher overall score ( $0.32$ , 95% CI =  $0.16$  to  $0.48$  per 1 kg/m<sup>2</sup> increase in BMI) and higher symptom subscores for wellbeing ( $0.02$ , 95% CI =  $0.00$  to  $0.04$ ) and tiredness ( $0.05$ , 95% CI =  $0.02$  to  $0.07$ ). Higher baseline NLR was associated with higher overall score ( $0.21$ , 95% CI =  $0.03$  to  $0.39$  per 1 unit increase in NLR) and higher symptom subscores wellbeing ( $0.03$ , 95% CI =  $0.01$  to  $0.05$ ) and nausea ( $0.03$ , 95% CI =  $0.02$  to  $0.05$ ). Baseline serum bicarbonate and phosphate did not demonstrate statistically significant associations with the overall ESASr:Renal score or for wellbeing, nausea, tiredness, or appetite subscores.

In the analysis assessing the association between ONS prescription and change in ESASr:Renal score, a range of 407 to 427 matched pairs were identified using propensity score matching over the 20 imputed data sets (Table 1). The

mean change in overall ESASr:Renal score was  $0.02$  (95% CI =  $-1.71$  to  $1.75$ ) among patients prescribed ONS, and  $-0.16$  (95% CI =  $-2.38$  to  $2.06$ ) among patients not prescribed ONS, over a median period of 127 days. There were no statistically significant associations between ONS prescription and change in ESASr:Renal for the overall score (beta coefficient for change in ESASr:Renal =  $0.17$ , 95% CI =  $-2.64$  to  $2.99$ ) and for subscores for appetite ( $-0.08$ , 95% CI =  $-0.56$  to  $0.39$ ), tiredness ( $-0.28$ , 95% CI =  $-0.74$  to  $0.18$ ), nausea ( $-0.18$ , 95% CI =  $-0.53$  to  $0.17$ ), and wellbeing ( $0.18$ , 95% CI =  $-0.28$  to  $0.64$ ).

## Discussion

To our knowledge, this is the first study assessing the association between ONS and patient-reported symptom burden among patients with advanced CKD-ND. There were weak associations between some nutritional lab parameters and ESASr:Renal subscores, and there was no statistically significant association between ONS prescription and change in ESASr:Renal subscores.

Symptom assessment and management have been identified by patients with advanced CKD as top research priorities.<sup>16</sup> Among the multiple physical and psychological symptoms experienced by patients with CKD, fatigue is one of the most common and has been established as a core

outcome measure among patients receiving HD.<sup>17,18</sup> The ESAS:Renal is a symptom assessment tool that has been validated for longitudinal assessment in patients with end-stage kidney disease.<sup>19</sup> Implementing ESAS:Renal in routine care has been shown to improve patient and provider symptom awareness and to empower patients to raise issues with providers.<sup>20</sup> Nutritional interventions, including ONS, are also an important part of symptom management among patients opting for conservative kidney management.<sup>21</sup>

In our study, the observed associations between nutrition-related variables and ESAS scores were of small magnitude and not clinically significant. Previous studies have established that the minimal clinically important difference for each ESAS subscore is 1 point.<sup>22</sup> The lack of clinically meaningful associations between biochemical parameters and symptom burden has been observed in previous studies of patients receiving dialysis, with negligible correlations between changes in biochemical markers and changes in ESAS:Renal.<sup>19</sup> However, composite nutrition scores, such as the Malnutrition Inflammation Score and Subjective Global Assessment, have demonstrated associations with quality-of-life domains in HD<sup>23-25</sup> and non-dialysis CKD.<sup>26</sup>

Despite the small magnitude of the associations between nutritional parameters and ESAS scores observed in our study, the directions of the effects are biologically plausible. Higher serum albumin was associated with lower overall symptom burden and lower tiredness and nausea subscores. Hypoalbuminemia often has multifactorial causes in patients with CKD, including malnutrition, inflammation, volume overload, and comorbidities.<sup>1</sup> In the Chronic Renal Insufficiency Cohort, patients with more severe gastrointestinal symptoms were more likely to have hypoalbuminemia.<sup>27</sup> Our study also found an association between higher BMI and worse overall symptom burden, tiredness, and wellbeing. Fatigue frequently occurs in people with obesity, and this association may be due to inflammation, sleep apnea, comorbidities, and psychiatric disorders.<sup>28</sup> A study that assessed different dimensions of fatigue found that obesity explained a significant portion of physical fatigue symptoms, even after adjustment for depression and inflammation.<sup>28</sup> Higher NLR was associated with worse overall ESAS score, wellbeing, and nausea. As a marker of inflammation, NLR has been associated with mortality, cardiovascular events, uremic toxin levels, and other inflammation markers.<sup>29,30</sup>

Although no studies have assessed the effect of ONS on symptom burden in patients with kidney disease, quality-of-life outcomes have been assessed in a few previous studies. One such study was conducted among patients with CKD-ND prescribed a low-protein diet; however, patients with malnutrition/PEW were excluded, and there was no control group.<sup>31</sup> In the HD population, there have been inconsistent results, with some studies demonstrating improved Short Form (SF)-36 scores for physical role functioning<sup>8,10</sup> with ONS

treatment, and 1 study that did not observe changes in any SF-36 domain.<sup>9</sup>

There are a few possible explanations for the lack of association between ONS and ESAS:Renal scores in our study. A previous analysis of prescription patterns in our population demonstrated that a majority of patients with CKD-ND prescribed ONS have infrequent use (1-2 ONS prescriptions per year).<sup>5</sup> The frequency of ESAS:Renal assessment in routine care (every 6 months or more frequently as indicated) may not capture effectively the short-term effects of ONS. We included time between ESAS measurements in the propensity score to account for the variability in this parameter.

Second, the effects of ONS on surrogate outcomes, such as nutritional lab parameters, may not translate directly to effects on patient-reported outcomes. Confounding pathways between the nutritional lab parameters and symptom burden may exist, and alternative pathways between the ONS intervention and symptom burden are also possible.<sup>32</sup> In addition, the multifactorial nature of CKD-related symptoms suggests that ONS alone may not be sufficient to alleviate symptoms. For example, fatigue may be caused by several factors, including depression, decreased oxygen delivery, decreased muscle mass/function due to metabolic derangements (acidosis, hyperphosphatemia, PEW), and sarcopenia.<sup>18</sup>

Finally, the ESAS:Renal outcome may not be a sensitive indicator of patient symptoms related to nutritional status. It is possible that other outcomes related to quality of life, such as SF-36 which has been studied in nutritional intervention trials<sup>8-10</sup> and the nutrition-specific quality-of-life instrument (NSQOL) which focuses on appetite and food enjoyment,<sup>26,33</sup> may better capture these patient-reported outcomes. This highlights the importance of the Standardized Outcomes in Nephrology (SONG) initiative in developing core outcomes of importance to patients with respect to CKD complications such as malnutrition and PEW.

One of the strengths of the study is the inclusion of a diverse patient population using a large provincial registry and standard protocols for management of malnutrition/PEW and assessment of symptom burden for patients with advanced CKD-ND. One limitation of our study is possible residual confounding. Owing to lack of registry data regarding nutritional scoring systems, such as subjective global assessment and malnutrition-inflammation-score, our analysis of nutritional status was limited to BMI and laboratory data. However, BMI is often difficult to interpret in patients with CKD due to edema or muscle wasting. Other laboratory parameters such as prealbumin, and other tools measuring body composition, such as bioimpedance or handgrip strength, may allow a more precise portrait of the nutritional state. However, these tools are not used by BC Renal dietitians in routine practice. Future prospective research is necessary to measure these parameters. The registry does not collect data on patient adherence to taking ONS. Our study is

limited to the subset of patients who completed ESASr:Renal assessments as per provincial guidelines (G5 CKD-ND and/or experiencing significant CKD-related symptoms)<sup>11</sup> and therefore cannot be extrapolated to all patients with CKD prescribed ONS.

In conclusion, this exploratory observational analysis of patients with advanced non-dialysis CKD demonstrated that nutrition-related parameters are associated with patient-reported symptoms, but we did not observe an association between ONS use and ESASr:Renal scores. Consensus surveys and workshops involving patients and other stakeholders can aid in determining optimal outcome measures to assess patient-reported symptom burden and functional status among patients with CKD and malnutrition/PEW. This process will then facilitate assessment of the effectiveness of ONS in prospective studies.

### Ethics Approval and Consent to Participate

This study was approved by the research ethics board at the University of British Columbia-Providence Health Care Institute (H19-01154).

### Consent for Publication

All authors provided their consent for publication.

### Availability of Data and Materials

The de-identified data underlying this article will be shared on reasonable request to the corresponding author.

### Acknowledgments

The authors acknowledge Ognjenka Djurdjev, BC Renal, the Patient Records and Outcome Management Information System team, the BC Renal Dietitians Group for their assistance and input with this project.




### Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: M.M.Y.W. has a consultancy agreement with George Clinical.

### Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by Michael Smith Health Research BC (M.M.Y.W., grant number 18465).

### ORCID iDs

Michelle M. Y. Wong  <https://orcid.org/0000-0002-1334-0763>  
 Mohammad Atiquzzaman  <https://orcid.org/0000-0002-0243-7666>  
 Dani Renouf  <https://orcid.org/0000-0002-6641-3292>

### Supplemental Material

Supplemental material for this article is available online.

### References

1. Fouque D, Kalantar-Zadeh K, Kopple J, et al. A proposed nomenclature and diagnostic criteria for protein–energy wasting in acute and chronic kidney disease. *Kidney Int.* 2008;73(4):391-398.
2. Rambod M, Bross R, Zitterkoph J, et al. Association of malnutrition-inflammation score with quality of life and mortality in hemodialysis patients: a 5-year prospective cohort study. *Am J Kidney Dis.* 2009;53(2):298-309.
3. Carrero JJ, Thomas F, Nagy K, et al. Global prevalence of protein-energy wasting in kidney disease: a meta-analysis of contemporary observational studies from the international society of renal nutrition and metabolism. *J Ren Nutr.* 2018;28(6):380-392.
4. Ikizler TA, Burrowes JD, Byham-Gray LD. KDOQI clinical practice guideline for nutrition in CKD: 2020 update. *Am J Kidney Dis.* 2020;76(3 suppl 1):S1-S107.
5. Wong MMY, Renouf D, Zheng Y, Sherif Z, Levin A. Nutritional Status, nutritional phenotypes, and oral nutritional supplement prescription patterns among patients with non-dialysis chronic kidney disease in British Columbia. *J Ren Nutr.* 2022;32(4):414-422.
6. Wong MMY, Zheng Y, Renouf D, Sherif Z, Levin A. Trajectories of nutritional parameters before and after prescribed oral nutritional supplements: a longitudinal cohort study of patients with chronic kidney disease not requiring dialysis. *Can J Kidney Health Dis.* 2022;9:20543581211069008. doi:10.1177/20543581211069008.
7. BC Renal Nutritional Supplement Policy. BC Renal pharmacy and formulary committee and the BC renal dietitians group. [http://www.bcrenal.ca/resource-gallery/Documents/Nutritional\\_Supplement\\_Policy-Program\\_Guideline.pdf](http://www.bcrenal.ca/resource-gallery/Documents/Nutritional_Supplement_Policy-Program_Guideline.pdf). Published September 2022. Accessed January 7, 2023.
8. Calegari A, Barros EG, Veronese FV, Thomé FS. Malnourished patients on hemodialysis improve after receiving a nutritional intervention. *J Bras Nefrol.* 2011;33(4):394-401.
9. Fouque D, McKenize J, de Mutsert R, et al. Use of a renal-specific oral supplement by haemodialysis patients with low protein intake does not increase the need for phosphate binders and may prevent a decline in nutritional status and quality of life. *Nephrol Dial Transplant.* 2008;23:2902-2910.
10. Scott MK, Shah NA, Vilay AM, et al. Effects of peridialytic oral supplements on nutritional status and quality of life in chronic hemodialysis patients. *J Ren Nutr.* 2009;19(2):145-152.
11. BCPRA Kidney Care Committee. Systematic symptom assessment & management (using the modified Edmonton Symptom Assessment System). <http://www.bcrenal.ca/resource-gallery/Documents/Systematic%20Symptom%20Assessment%20and%20Management%20Guideline.pdf>. Published May 2017. Accessed January 6, 2022.
12. Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. New York, NY: John Wiley; 2004.
13. Deb S, Austin PC, Tu JV, et al. A Review of propensity-score methods and their use in cardiovascular research. *Can J Cardiol.* 2016;32(2):259-265.
14. Leyrat C, Seaman SR, White IR, et al. Propensity score analysis with partially observed covariates: how should multiple imputation be used? *Stat Methods Med Res.* 2019;28(1):3-19. doi:10.1177/0962280217713032.

15. Granger E, Sergeant JC, Lunt M. Avoiding pitfalls when combining multiple imputation and propensity scores. *Stat Med*. 2019;38(26):5120-5132. doi:10.1002/sim.8355.
16. Manns B, Hemmelgarn B, Lillie E, et al. Setting research priorities for patients on or nearing dialysis. *Clin J Am Soc Nephrol*. 2014;9:1813-1821.
17. Gregg LP, Bossola M, Ostrosky-Frid M, Hedayati SS. Fatigue in CKD: epidemiology, pathophysiology, and treatment. *Clin J Am Soc Nephrol*. 2021;16(9):1445-1455.
18. Ju A, Teixeira-Pinto A, Tong A, et al. Validation of a core patient-reported outcome measure for fatigue in patients receiving hemodialysis. *Clin J Am Soc Nephrol*. 2020;15(11):1614-1621.
19. Davison SN, Jhangri GS, Johnson JA. Longitudinal validation of a modified Edmonton Symptom Assessment System (ESAS) in haemodialysis patients. *Nephrol Dial Transplant*. 2006;21(11):3189-3195.
20. Evans JM, Glazer A, Lum R, et al. Implementing a patient-reported outcome measure for hemodialysis patients in routine clinical care: perspectives of patients and providers on ESAS-renal. *Clin J Am Soc Nephrol*. 2020;15(9):1299-1309.
21. Stevenson J, Meade A, Randall AM, et al. Nutrition in renal supportive care: patient-driven and flexible. *Nephrology*. 2017;22(10):739-747.
22. Hui D, Bruera E. The Edmonton Symptom Assessment System 25 years later: past, present, and future developments. *J Pain Symptom Manage*. 2017;53(3):630-643.
23. Kelly OJ, Huang M-C, Liao H-Y, et al. A low-protein diet with a renal-specific oral nutrition supplement helps maintain nutritional status in patients with advanced chronic kidney disease. *J Pers Med*. 2021;11(12):1360.
24. de Roij van Zuijdewijn CL, Grooteman MP, Bots ML, et al. Comparing tests assessing protein-energy wasting: relation with quality of life. *J Ren Nutr*. 2016;26(2):111-117. doi:10.1053/j.jrn.2015.09.003.
25. Vero LM, Byham-Gray L, Parrott JS, Steiber AL. Use of the subjective global assessment to predict health-related quality of life in chronic kidney disease stage 5 patients on maintenance hemodialysis. *J Ren Nutr*. 2013;23(2):141-147.
26. Feasel-Aklilu S, Marcus A, Parrott JS, Peters E, Byham-Gray L. Is nutrition specific quality of life associated with nutritional status? *J Ren Nutr*. 2018;28(4):283-291.
27. Zhang X, Bansal N, Go AS, et al. Gastrointestinal symptoms, inflammation and hypoalbuminemia in chronic kidney disease patients: a cross-sectional study. *BMC Nephrol*. 2015;16:211. doi:10.1186/s12882-015-0209-z.
28. Lim W, Hong S, Nelesen R, Dimsdale JE. The association of obesity, cytokine levels, and depressive symptoms with diverse measures of fatigue in healthy subjects. *Arch Intern Med*. 2005;165(8):910-915.
29. Pineault J, Lamarche C, Bell R, et al. Association of neutrophil-to-lymphocyte ratio with inflammation and erythropoietin resistance in chronic dialysis patients. *Can J Kidney Health Dis*. 2017;4:2054358117735563. doi:10.1177/2054358117735563.
30. Lano G, Sallée M, Pelletier M, et al. Neutrophil: lymphocyte ratio correlates with the uremic toxin indoxyl sulfate and predicts the risk of death in patients on hemodialysis. *Nephrol Dial Transplant*. 2022;37(12):2528-2537. doi:10.1093/ndt/gfab350.
31. Campbell KL, Ash S, Bauer JD. The impact of nutrition intervention on quality of life in pre-dialysis chronic kidney disease patients. *Clin Nutr*. 2008;27(4):537-544.
32. Scialla JJ, Kendrick J, Uribarri J, et al. State-of-the-art management of hyperphosphatemia in patients with CKD: an NKF-KDOQI controversies perspective. *Am J Kidney Dis*. 2021;77(1):132-141.
33. Han H, Burrowes JD, Houser R, et al. What is the impact of nutritional status on health-related quality of life in hemodialysis patients? *J Ren Nutr*. 2012;22:237-243.