Gdański Uniwersytet Medyczny

Wydział Lekarski

Rozprawa doktorska

„Ocena częstości występowania objawów z dolnego odcinka przewodu pokarmowego i ich związku z jakością życia oraz wybranymi parametrami kliniczno-laboratoryjnymi u pacjentów z przewlekłą chorobą nerek”

lek. Jakub Ruszkowski

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Spis treści

Wykaz prac naukowych wchodzących w skład cyklu publikacji będącego podstawą rozprawy doktorskiej

1. J. Ruszkowski, Z. Heleniak, E. Król, A. Tarasewicz, J. Gałgowska, J. M. Witkowski, A. Dębska-Ślizień: Constipation and the quality of life in conservatively treated chronic kidney disease patients: a cross-sectional study. International Journal of Medical Sciences. 2020; 17 (18): 2954-2963.

   (Impact Factor: 3,738; punktacja MEiN: 70)

2. J. Ruszkowski, Z. Heleniak, E. Król, A. Tarasewicz, J. M. Witkowski, A. Dębska-Ślizień: Associations between symptoms of constipation and sleep quality in patients with nondialysis chronic kidney disease: a cross-sectional study. Polish Archives of Internal Medicine. 2021; 131 (6): 512-519.

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Wykaz skrótów używanych w rozprawie doktorskiej

BSFS – bristolska skala uformowania stolca (ang. *Bristol Stool Form Scale*)

CI – przedział ufności (ang. *confidence interval*)

eGFR – szacowany wskaźnik przesączania kłębuszkowego (ang. *estimated glomerular filtration rate*)

FODMAP – fermentujące oligo-, di- i monosacharydy oraz poliole (ang. *fermentable oligosaccharides, disaccharides, monosaccharides and polyols*)

HDL-C – cholesterol lipoprotein o wysokiej gęstości (ang. *high-density lipoprotein-cholesterol*)

HR – współczynnik hazardu, inaczej: iloraz hazardu, iloraz zagrożeń lub względny hazard (ang. *hazard ratio*)

HRQoL – jakość życia zależna od stanu zdrowia (ang. *health-related quality of life*)

IBS – zespół jelita drażliwego (ang. *irritable bowel syndrome*)

IBS-C – zaparciowa postać zespołu jelita drażliwego (ang. *irritable bowel syndrome with predominant constipation*)

ICD – Międzynarodowa Statystyczna Klasyfikacja Chorób i Problemów Zdrowotnych (ang. *International Statistical Classification of Diseases and Related Health Problems*)

MOS-Sleep-R – kwestionariusz *Medical Outcomes Study 12-item Sleep Scale-Revised*

OR – iloraz szans (ang. *Odds ratio*)

PAC-SYM – kwestionariusz *The Patient Assessment of Constipation-Symptoms*

PChN – przewlekła choroba nerek

PR – współczynnik prewalencji (ang. *prevalence ratio*)

PROSPERO – Międzynarodowy Prospektywny Rejestr Przeglądów Systematycznych (ang. *International Prospective Register of Systematic Reviews*)

SF-36v2 – kwestionariusz *The 36-Item Short Form Health Survey version 2*

SIBO – zespół rozrostu bakteryjnego jelita cienkiego (ang. *small intestinal bacterial overgrowth*)

5-HT_4 – receptor serotoninowy 4

Streszczenie

Szacuje się, że około co dziesiąta osoba na świecie obciążona jest przewlekłą chorobą nerek (PChN). Chorujący na nią pacjenci doświadczają wielu objawów, w tym dolegliwości z dolnego odcinka przewodu pokarmowego, których rozpowszechnienie, nasilenie, patogeneza ani konsekwencje nie zostały systematycznie przeanalizowane przed przeprowadzeniem badań wchodzących w skład niniejszej dysertacji.

W ramach projektu doktorskiego przeprowadzono dwa spójne tematycznie badania, których szczegółowy opis został przedstawiony w trzech opublikowanych artykułach i dołączonych do nich materiałach dodatkowych.

Celem badania przekrojowego pacjentów zgłaszających się na rutynową wizytę w Poradni Nefrologicznej Uniwersyteckiego Centrum Klinicznego w Gdańsku było określenie wśród niedializowanych pacjentów z PChN: (1) rozpowszechnienia zaparcia i związanych z nim objawów, (2) czynników związanych ze zróżnicowanym rozpowszechnieniem zaparcia i związanych z nim objawów, (3) relacji między występowaniem zaparcia i związanych z nim objawów a jakością życia i snu. Na kolejnym etapie projektu doktorskiego rozszerzono zarówno zakres objawów, jak i badaną populację – przygotowano przegląd systematyczny prac oryginalnych pochodzących z różnych części świata. Jego celem było oszacowanie rozpowszechnienia i nasilenia objawów z dolnego odcinka przewodu pokarmowego u niedializowanych pacjentów z PChN, jak również identyfikacja związków między ich występowaniem lub nasileniem a jakością życia związaną ze zdrowiem (HRQoL), wynikami testów laboratoryjnych lub danymi klinicznymi. Do badania przekrojowego zrekrutowano 111 pacjentów, natomiast do przeglądu systematycznego włączono 37 badań.

Do najczęściej zgłaszanych objawów z dolnego odcinka przewodu pokarmowego u ankietowanych pacjentów z ośrodka gdańskiego należały: wzdęcie (51%), napinanie się i wysiłek w celu wypróżnienia (43%), zbyt twardy stolec (39%), dyskomfort w brzuchu (37%)

i poczucie niezupełnego wypróżnienia (35%). Zwykle zgłaszane objawy miały łagodne nasilenie. Im gorsza była funkcja filtracyjna nerek, tym większe było nasilenie bolesnego wypróżniania, napinania się i wysiłku w celu wypróżnienia, poczucia niepełnego wypróżnienia oraz zbyt twardego stolca. Dyskomfort w brzuchu okazał się niezależnie związany z gorszą oceną wszystkich ocenianych domen HRQoL i większym rozpowszechnieniem obniżonej jakości snu.

W badaniu przekrojowym zaparcie czynnościowe stwierdzono u blisko 19% ankietowanych. W wyniku wieloczynnikowej analizy stwierdzono, że objawy zaparcia czynnościowego występowały istotnie częściej u pacjentów przyjmujących paracetamol, a rzadziej u pacjentów przyjmujących niesteroidowe leki przeciwzapalne. Potwierdzono również związek między obecnością objawów zaparcia czynnościowego a gorszą oceną HRQoL (m.in. pacjenci ci uskarżali się na większe dolegliwości bólowe i mniejszą witalność niż pacjenci z PChN bez zaparcia czynnościowego) i gorszą jakością snu. Jak wykazano w przygotowanym przeglądzie systematycznym, rozpowszechnienie zaparcia czynnościowego w PChN było rzadko oceniane w opublikowanych dotąd pracach. Zdecydowanie częściej dotychczasowe badania podejmowały temat rozpowszechnienia i nasilenia zaparcia samodzielnie rozpoznawanego u siebie przez pacjentów. Jak wykazano w przeprowadzonych w ramach doktoratu metaanalizach, średnie rozpowszechnienie tak rozumianego zaparcia wynosiło od 30% w stadium G3 do 39% w stadiach G4–5 przewlekłej choroby nerek.

W niniejszej dysertacji zwrócono szczególną uwagę na elementy wchodzące w skład doświadczenia zaparcia przez pacjenta, w tym twarde uformowanie stolca oraz niską częstość wypróżnień. W badaniu przekrojowym twarda konsystencja stolca (typ 1–2 w bristolskiej skali uformowania stolca) występowała u 29% ankietowanych. Wykazano, że przyjmowanie diuretyków było związane z większym rozpowszechnieniem zgłaszania twardego stolca. W metaanalizie wyników pochodzących z czterech publikacji oszacowano, że średnie

rozpowszechnienie takiego uformowania stolca wynosiło od blisko 15% w stadiach G1–2 do 24,5% w stadiach G4–5 przewlekłej choroby nerek. Częstszym zjawiskiem okazało się wypróżnianie rzadziej niż raz dziennie, jednak ilość dostępnych danych na ten temat jest bardzo ograniczona; przeprowadzone badanie przekrojowe okazało się jedynym źródłem danych o częstości wypróżnień u pacjentów z PChN w stadiach G1–3.

Nasilenie rozpoznanego samodzielnie zaparcia było konsekwentnie powiązane z niższą HRQoL w przeprowadzonych dotąd badaniach rekrutujących niedializowanych pacjentów z PChN. Jak wykazano w przeprowadzonym badaniu przekrojowym, pacjenci wypróżniający się rzadziej niż raz dziennie gorzej oceniali swoją jakość życia w zakresie kilku domen, w tym jakości snu, w porównaniu z pacjentami wypróżniającymi się codziennie. W przeciwieństwie do częstości wypróżnień, zgłaszanie twardej konsystencji stolca nie było istotnie związane z gorszą oceną HRQoL ani jakości snu.

Wyniki przeprowadzonych w ramach projektu doktorskiego badań mogą pozytywnie oddziaływać zarówno na praktykę kliniczną, jak i na dalszy rozwój nauki. Udokumentowanie znacznego rozpowszechnienia oraz istotnych implikacji objawów z dolnego odcinka przewodu pokarmowego w PChN może motywować przedstawicieli zawodów medycznych do aktywnego poszukiwania dolegliwości z przewodu pokarmowego u chorych, a w razie ich stwierdzenia – do podejmowania działań terapeutycznych. Ponadto dzięki wskazaniu w przygotowanym przeglądzie systematycznym braków danych o patofizjologii i następstwach klinicznych objawów z dolnego odcinka przewodu pokarmowego, a także ograniczeń metodycznych dotychczasowych badań, niniejsza dysertacja może posłużyć do projektowania właściwie ukierunkowanych, wysokiej jakości badań poszerzających rozumienie patogenezy i implikacji omawianych tu objawów.

Streszczenie w języku angielskim

It is estimated that approximately one in ten people worldwide has chronic kidney disease (CKD). Affected patients experience a range of symptoms, including lower gastrointestinal (GI) complaints, the prevalence, severity, pathogenesis, and consequences of which had not been systematically analysed prior to the studies included in this dissertation.

Two thematically coherent studies were conducted as part of this doctoral project, the details of which are presented in three published articles and the accompanying supplementary materials.

The aim of the cross-sectional study of patients presenting for a routine visit to the Nephrology Clinic, University Clinical Centre, Gdańsk, Poland, was to determine the following among non-dialysis patients with CKD: (1) the prevalence of constipation and related symptoms, (2) factors associated with the differential prevalence of constipation and related symptoms, (3) the relationship between the prevalence of constipation and related symptoms on the one hand and the quality of life and sleep on the other. In the next stage of this doctoral project, both the range of symptoms and the study population were expanded, and a systematic review of original papers from different parts of the world was prepared. Its aim was to estimate the prevalence and severity of lower GI symptoms in non-dialysis patients with CKD and to identify associations between their occurrence or their severity on the one hand and health-related quality of life (HRQoL), laboratory test results or clinical data on the other. A total of 111 patients were recruited for the cross-sectional study, and 37 studies were included in the systematic review.

The most commonly reported lower GI symptoms in the surveyed patients from the Gdańsk site included bloating (51%), straining/squeezing to pass bowel movement (43%), too hard stool (39%), abdominal discomfort (37%) and feeling of incomplete bowel movement (35%). Typically, the reported symptoms were of mild severity. The lower the renal filtration

function was, the greater the severity of painful defecation, straining/squeezing to pass bowel movement, feeling of incomplete bowel movement, and too hard stools. Abdominal discomfort was found to be independently associated with poorer scores on all the assessed HRQoL domains and a higher prevalence of reduced sleep quality.

In the cross-sectional study, functional constipation was found in nearly 19% of the respondents. Multivariate analysis revealed that symptoms of functional constipation were significantly more common in patients taking paracetamol and less common in patients taking non-steroidal anti-inflammatory drugs. An association was also confirmed between the presence of functional constipation symptoms on the one hand and poorer HRQoL scores (among other things, those patients complained of more pain and lower vitality than CKD patients without functional constipation) and poorer sleep quality on the other. As demonstrated in the systematic review, the prevalence of functional constipation in CKD has rarely been assessed in the studies published to date. Far more often, studies to date have addressed the prevalence and severity of self-reported constipation in patients. As shown in the meta-analyses conducted as part of this doctoral project, the average prevalence of so defined constipation ranged from 30% in stage G3 to 39% in stages G4–5 of CKD.

In this dissertation, particular attention was paid to the elements that comprise a patient's experience of constipation, including hard stool consistency and low frequency of bowel movements. In the cross-sectional study, hard stool consistency (type 1–2 on the Bristol Stool Form Scale) was present in 29% of the respondents. Treatment with diuretics was shown to be associated with a higher prevalence of reporting hard stools. A meta-analysis of the results from 4 publications estimated that the mean prevalence of this stool consistency ranged from nearly 15% in stages G1–2 to 24.5% in stages G4–5 of CKD. Having a bowel movement less than once a day appeared to be more common, but the amount of data available on this topic is very

limited; the cross-sectional study appeared to be the only source of data on the frequency of bowel movements in patients with CKD stages G1–3.

The severity of self-reported constipation has been consistently associated with lower HRQoL in the studies recruiting non-dialysis patients with CKD that have been conducted to date. As shown in the cross-sectional study, patients having bowel movements less than once a day rated their quality of life lower in several domains, including sleep quality, compared with patients having daily bowel movements. In contrast to the frequency of bowel movements, the reporting of hard stool consistency showed no significant association with lower HRQoL or sleep quality scores.

The findings of this doctoral project have the potential to positively impact both clinical practice and further scientific development. The documentation of the significant prevalence and important implications of lower GI symptoms in CKD may motivate health professionals to actively seek out GI complaints in patients and, if identified, to institute appropriate treatment. Furthermore, by pointing out, in the systematic review, the gaps in data on the pathophysiology and clinical implications of lower GI symptoms, as well as the methodological limitations of the previous studies, this dissertation can serve to design well-targeted, high-quality studies to broaden our understanding of the pathogenesis and implications of the symptoms discussed herein.

1. Wstęp

1.1. Przewlekła choroba nerek i towarzyszące jej objawy z przewodu pokarmowego

Przewlekła choroba nerek (PChN) to utrzymujące się powyżej trzech miesięcy nieprawidłowości budowy lub czynności nerek mające znaczenie dla zdrowia [1, 2]. PChN jest powszechną chorobą dotyczącą około 9,1% populacji światowej i 10,8% populacji dorosłych Polaków [3, 4]. W konsekwencji samej choroby, a także działań niepożądanych i powikłań stosowanych metod leczenia, pacjenci z PChN doświadczają wielu objawów [5, 6], które istotnie obniżają ich jakość życia zależną od stanu zdrowia (ang. *health-related quality of life*, HRQoL) [6–8].

Spośród licznych objawów występujących u pacjentów z PChN szczególne zainteresowanie badaczy w ostatnich latach budzą objawy z przewodu pokarmowego. Dotychczasowe przeglądy systematyczne literatury naukowej na temat symptomatologii PChN u pacjentów niedializowanych wymieniały jedynie nieliczne objawy z przewodu pokarmowego, oparte były na małej liczbie badań obserwacyjnych, a część z nich stosowała nieodpowiednie metody statystyczne [5, 9]. Jak dotąd opublikowano tylko jeden przegląd systematyczny w pełni poświęcony rozpowszechnieniu objawów z przewodu pokarmowego u pacjentów dializowanych [10]; brak było podobnych opracowań dotyczących chorych niedializowanych.

O ile w literaturze medycznej z XIX wieku to biegunka była często opisywanym objawem mocznicowym [11–13], aktualnie – co można częściowo tłumaczyć mniejszym rozpowszechnieniem ciężkich powikłań mocznicy – więcej uwagi poświęca się zaparciu. Dotychczasowe duże badania epidemiologiczne (głównie rejestrowe) wskazują, że występowanie zaparcia może być związane ze zwiększonym zagrożeniem (tj. hazardem w rozumieniu statystycznym) nie tylko zachorowalności na PChN i niewydolność nerek, lecz także takich punktów końcowych jak incydent sercowo-naczyniowy i zgon z jakiejkolwiek przyczyny w różnych populacjach pacjentów [14–17]. W badaniu populacji ponad 3,5 mln

amerykańskich weteranów z wyjściowo prawidłową funkcją nerek (eGFR ≥ 60 ml/min/1,73 m^2) osoby z zaparciem charakteryzowały się w porównaniu z osobami bez tego objawu istotnie wyższą zachorowalnością na PChN [skorygowany współczynnik hazardu, HR: 1,13 (95% CI: 1,11–1,14)] i niewydolność nerek (skorygowany HR: 1,09; 95% CI: 1,01–1,18) oraz szybszym spadkiem eGFR [18]. Z kolei Lu i wsp. zaobserwowali, że pojawienie się zaparcia *de novo* u pacjentów z PChN mieszkających w Tajwanie związane było z istotnie wyższą zapadalnością na niewydolność nerek [skorygowany HR: 1,90 (95% CI: 1,60–2,27)] [19]. Ponadto w wieloośrodkowym badaniu retrospektywnym przeprowadzonym w Tajwanie zaobserwowano, że istotne problemy z dojrzewaniem przetoki tętniczo-żylnej częściej występowały wśród pacjentów z niewydolnością nerek (stadium G5 i G5D) przyjmujących kontaktowe leki przeczyszczające niż u pacjentów nieprzyjmujących takich leków (skorygowany iloraz szans, OR: 1,63; 95% CI 1,17–2,26; P = 0,004) [20]. W innym badaniu obejmującym ponad 12 tys. pacjentów hemodializowanych obserwowanych do trzech lat wykazano związek między przyjmowaniem leków przeczyszczających a zwiększonym hazardem zgonu z jakiejkolwiek przyczyny [skorygowany HR: 1,12 (95% CI: 1,03–1,21)] [21].

Zasadniczym problemem przytoczonych badań rejestrowych jest wykorzystanie niebezpośrednich, zastępczych (ang. *surrogate*) metod oceny wystąpienia zaparcia u pacjenta (analiza kodów ICD-9 lub -10 z dokumentacji medycznej pacjenta; rozpoznanie zaparcia w oparciu o przepisywanie pacjentowi lub wykupywanie przez niego leków przeczyszczających). Z tego powodu część pacjentów doświadczających objawu, ale nieposzukujących pomocy medycznej, może być w nich błędnie zaklasyfikowana jako niedoświadczająca objawu. Co więcej, wykorzystanie takich niebezpośrednich metod może skutkować problemami interpretacyjnymi. Przykładowo: w przypadku związku między wystąpieniem punktu końcowego a przyjmowaniem leków przeczyszczających wystąpienie

punktu końcowego można interpretować również jako działanie niepożądane podjętego leczenia.

Istotnym utrudnieniem w prawidłowym oszacowaniu rozpowszechnienia takich objawów jak zaparcie czy biegunka są także rozbieżności w stosowanych definicjach i odmiennym rozumieniu terminologii medycznej przez pacjentów i pracowników ochrony zdrowia (omówione w kolejnym podrozdziale) [22–25].

1.2. Zaparcie: Problematyczność terminologii, spektrum objawów i ich znaczenie

Jak słusznie zauważył prof. dr hab. n. med. Andrzej Dąbrowski, „przedstawienie uniwersalnej definicji [zaparcia] jest trudne, gdyż określenie to ma różne znaczenia dla różnych ludzi" [26]. Odmienne rozumienie zaparcia przez pacjentów i klinicystów [23–25] oraz istnienie różnych definicji zaparcia w dostępnej literaturze sprawiają, że szacunki rozpowszechnienia przewlekłego zaparcia w ogólnej populacji europejskiej wahają się od 4,1% do 39,6% [27]. Przy porównaniu różnych kryteriów rozpoznania, zaparcie rozpoznane samodzielnie przez pacjenta (ang. *self-reported constipation*) występuje częściej niż zaparcie rozumiane jako wypróżnianie rzadziej niż trzy razy tygodniowo [22, 27].

Zaparcie może mieć charakter pierwotny lub wtórny. W oparciu o czynnościową diagnostykę anorektalną i ocenę szybkości pasażu jelitowego Amerykańskie Stowarzyszenie Gastroenterologiczne (ang. *American Gastroenterological Association*) wyróżnia trzy typy zaparcia pierwotnego: zaparcie z prawidłowym pasażem jelitowym, zaparcie ze zwolnionym pasażem jelitowym oraz zaburzenie defekacji (zwane również zaburzeniem ewakuacji stolca lub dysfunkcją dna miednicy) [28]. Inne podejście do klasyfikacji pierwotnego zaparcia znalazło odzwierciedlenie w Kryteriach Rzymskich IV. Opiera się ona przede wszystkim na podawanych przez pacjenta dolegliwościach, na podstawie których rozpoznaje się zaparcie czynnościowe lub zaparciową postacią zespołu jelita drażliwego (ang. *irritable bowel syndrome with predominant constipation*, IBS-C) [29]. Wyżej wspomniana diagnostyka czynnościowa

w Kryteriach Rzymskich IV służy do różnicowania czynnościowych zaburzeń defekacji [30]. Ustalenie elementów składających się na doświadczenie zaparcia może ułatwić identyfikację mechanizmów patofizjologicznych odpowiadających za zgłaszane objawy, jak również posłużyć wyborze optymalnej metody leczenia. W przeglądzie systematycznym kwestionariuszy używanych do oceny objawów zaparcia zidentyfikowano aż 30 różnych elementów [31]. Elementy oceniane w przynajmniej dwóch spośród osiemnastu różnych kwestionariuszy ujętych w wyżej wymienionym przeglądzie zebrano w tabeli 1.

Tabela 1. Wyciąg elementów kwestionariuszy używanych do oceny zaparcia.

Objawy związane z jamą brzuszną (*Abdominal symptoms*)	Ból brzucha (*Pain*)
	Wzdęcie (*Bloating*)
	Dyskomfort (*Discomfort*)
	Gazy (*Gas*)
	Uczucie ściskania/skurczów w brzuchu (*Cramping*)
Objawy związane z wypróżnianiem (*Bowel movement-related symptoms*)	Poczucie niepełnego wypróżnienia (*Incomplete evacuation*)
	Częstość wypróżnień (*Frequency*)
	Wysiłek/parcie (*Straining*)
	Poczucie braku możliwości wypróżnienia (*Inability to pass*)
	Ból w trakcie wypróżniania (*Ease/pain during bowel movement*)
	Nagła potrzeba wypróżnienia (*Urgency*)
Objawy związane ze stolcem (*Stool-related symptoms*)	Konsystencja (*Consistency*)
	Ilość (*Amount*)
Objawy związane z odbytnicą i odbytem (*Anal/rectal symptoms*)	Ból odbytu (*Pain*)
	Krwawienie z odbytu (*Bleeding*)
	Poczucie przeszkody w odbycie lub odbytnicy (*Anus blockage*)
Inne (*Others*)	Korzystanie z leków przeczyszczających lub lewatyw (*Use of laxatives/enemas*)
	Konieczność ręcznego wspomagania wypróżnienia (*Use of digital manoeuvres*)
	Czas spędzany w toalecie (*Time spent in toilet*)
	Historia choroby: okres trwania zaparcia (*History: duration of constipation*)

Zmodyfikowana tabela 3 pt. „Summary of Questionnaire Items in Patient-reported Outcome Measures Measuring Constipation Symptoms" z pracy V. Vien Lee i wsp. [31]. Modyfikacja (JR) polegała na usunięciu elementów występujących w < 2 kwestionariuszach.

Zależność między obrazem klinicznym a mechanizmem patofizjologicznym wykazano wielokrotnie w przypadku konsystencji i uformowania stolca ocenianych za pomocą bristolskiej skali uformowania stolca (ang. *Bristol Stool Form Scale*, BSFS). Korelują one z czasem pasażu jelitowego, zwłaszcza u objawowych pacjentów: im kał jest twardszy/bardziej grudkowaty, tym wolniejszy jest pasaż jelitowy [32–35]. BSFS może służyć również do identyfikacji pacjentów ze zwolnionym pasażem jelita grubego [34–37]. Co ciekawe, czas pasażu jelitowego silniej koreluje z konsystencją i uformowaniem stolca (ocenianymi przy pomocy BSFS) niż z częstością wypróżnień; część badań zupełnie podważa istotność ostatniej korelacji [33–36].

Przegląd systematyczny prac opublikowanych do kwietnia 2019 roku wskazuje, że objawy zwykle kojarzone z zaburzeniami defekacji (np. wzmożone parcie na stolec [26]) nie rozróżniają wiarygodnie pacjentów z obiektywnie potwierdzonymi zaburzeniami defekacji od pacjentów bez takich zaburzeń [38]. Jedynie u pacjentów z prawidłowym pasażem jelitowym zgłoszenie poczucia przeszkody/blokady w obrębie odbytu i odbytnicy (wskaźnik wiarygodności zgłoszenia objawu: 2,2) oraz stosowanie ręcznych manewrów w celu oddania stolca (wskaźnik wiarygodności zgłoszenia objawu: 3,2) może przemawiać za rozpoznaniem zaburzeń defekacji [38]. W tej samej grupie pacjentów wykluczenie poczucia niepełnego wypróżnienia przemawia przeciwko rozpoznaniu zaburzeń defekacji (wskaźnik wiarygodności niezgłoszenia objawu: 0,4) [38].

Jak wspomniano wyżej, sprecyzowanie elementów wchodzących w skład spektrum doświadczenia zaparcia pozwala nie tylko na wskazanie mechanizmów mogących stać za objawami, lecz także na dobór właściwej terapii. Wykazano, że pacjenci z zaparciem czynnościowym lub z IBS-C, u których współistnieje wzdęcie, charakteryzują się niższą satysfakcją z leczenia [39]. Stąd też ujawnienie tego objawu jest istotne w trakcie optymalizacji farmakoterapii zaparcia. Z jednej strony przeczyszczające leki osmotycznie czynne, przede

wszystkim laktuloza, mogą nasilać wzdęcie. Z drugiej strony istnieją leki stosowane w zaparciu, w przypadku których wykazano łagodzenie wzdęcia: linaklotyd (agonista receptora cyklazy guanylanowej-C), lubiproston (aktywator kanału chlorkowego typu 2 na szczytowej części błony komórkowej enterocyta), prukalopryd (wybiórczy agonista receptora 5-HT_4) i tenapanor (inhibitor wymiennika sodowo-protonowego typu 3) [40, 41].

1.3. Związek objawów z przewodu pokarmowego z jakością życia i snu

Osoby spełniające kryteria rozpoznania zaburzeń czynnościowych przewodu pokarmowego (zgłaszające objawy zgodnie z Kryteriami Rzymskimi IV) charakteryzują się niższą HRQoL, zarówno w zakresie wymiaru psychicznego, jak i fizycznego, w porównaniu z osobami nieprezentującymi objawów zaburzeń czynnościowych [42]. Nie wykazano istotnych różnic w jakości życia między pacjentami z zaparciem czynnościowym, biegunką czynnościową, czy wzdęciem czynnościowym [43]. Gorszą jakość życia obserwuje się jednak w przypadku współwystępowania kilku zaburzeń czynnościowych przewodu pokarmowego, zwłaszcza obejmujących różne jego odcinki [44, 45]. Z przeglądu systematycznego, do którego włączono badania oceniające HRQoL u pacjentów z zaparciem czynnościowym (Kryteria Rzymskie I-III), wynika, że w porównaniu ze zdrową populacją pacjenci ci gorzej oceniają zwłaszcza swoje zdrowie ogólne (ang. *general health*), funkcjonowanie społeczne (ang. *social functioning*) i własne zdrowie psychiczne (ang. *mental health*) [46]. U pacjentów dializowanych, podobnie jak w populacji ogólnej, wykazano związek między występowaniem zaparcia czynnościowego a niższą HRQoL, jednak ilość i jakość danych w tym przypadku jest mniejsza [47, 48].

Obniżoną jakość życia obserwuje się jednakże nie wyłącznie u pacjentów spełniających kryteria rozpoznania czynnościowych zaburzeń przewodu pokarmowego. Szereg badań jakościowych dowodzi, że starsze osoby uskarżające się na zaparcie zgłaszają nie tylko towarzyszące temu inne dolegliwości fizyczne (jak w tabeli 1), lecz także dotkliwe, negatywne

implikacje psychologiczne i społeczne [49, 50]. Dotychczasowe badania wskazują na podobny związek z gorszą jakością życia również w przypadku nietrzymania stolca [51–54], a mniej liczne badania – w przypadku wzdęcia [55, 56].

Intrygującym, nadal nie w pełni zrozumianym odkryciem, jest związek między częstszym występowaniem objawów z przewodu pokarmowego a zaburzeniami lub obniżoną jakością snu. Metaanaliza 36 badań opublikowana w 2018 roku wykazała, że zaburzenia snu występują częściej u pacjentów z IBS niż u osób bez takich zaburzeń (OR 2,62; 95% CI 2,05–3,34) i dotyczą średnio 37,6% (95% CI: 31,4%–44,3%) pacjentów [57]. Kolejna metaanaliza dziesięciu badań potwierdziła częstsze występowanie zaburzeń snu u pacjentów z dyspepsją czynnościową niż u osób bez takich zaburzeń (OR 2,88; 95% CI: 2,52-3,30) [58]. W literaturze można znaleźć potwierdzenie istotnie częstszego występowania nadmiernej senności w trakcie dnia u pacjentów z takimi zaburzeniami czynnościowymi jak dyspepsja przypominająca chorobę wrzodową (ang. *ulcer-like dyspepsia*, odpowiednik zespołu bólu w nadbrzuszu (ang. *epigastric pain syndrome*) począwszy od Kryteriów Rzymskich III), biegunkowa i naprzemienna (bliski odpowiednik „mieszanej" począwszy od Kryteriów Rzymskich III) postać IBS oraz zaparcie czynnościowe [59]. W badaniu obejmującym 3000 dorosłych Japończyków zgłaszających zaparcie stwierdzono, że zarówno osoby z twardą/grudkową konsystencją stolca (typ 1 i 2 w BSFS), jak i osoby zgłaszające objawy stanowiące kryteria rozpoznania zaparcia czynnościowego, istotnie częściej oceniają swój sen negatywnie niż pozytywnie [60].

Bouchoucha i wsp. w swoich analizach odwrócili kierunek wnioskowania przyczynowo-skutkowego [61]. Opisali oni, że u osób z bezsennością istotnie częściej obserwuje się zaparcie lub wzdęcie czynnościowe niż u osób bez zaburzeń snu [61]. Częstsze występowanie zaparcia (tym razem samodzielnie rozpoznanego przez pacjenta) u osób z bezsennością zaobserwowano także w dużym badaniu obejmującym 17 529 pracowników

zmianowych z Korei Południowej; wykazano w nim również zależność między nasileniem bezsenności a zwiększającą się szansą występowania zaparcia (ang. *dose-response relationship*) [62]. Bouchoucha i wsp. odnotowali także, że u osób z nadmierną sennością częściej niż u osób zdrowych obserwuje się czynnościową biegunkę [61]. Ponadto, w porównaniu z osobami bez zaburzeń snu, zarówno u osób z bezsennością, jak i nadmierną sennością w trakcie dnia, Bouchoucha i wsp. istotnie częściej rozpoznawali napadowy ból odbytu/odbytnicy (ang. *proctalgia fugax*) [61].

Według danych literaturowych pacjenci z PChN charakteryzują się podwyższonym ryzykiem wystąpienia wszystkich wymienionych powyżej problemów: objawów z przewodu pokarmowego, zaburzeń snu i obniżonej jego jakości, a także obniżonej HRQoL. Pomimo prawdopodobnego istnienia sieci powiązań między wspomnianymi objawami i zaburzeniami, do czasu niniejszej dysertacji nie analizowano zależności między ww. czynnikami.

1.4. Postępowanie niefarmakologiczne i leki stosowane w zaparciu – właściwości nefroprotekcyjne

W leczeniu pierwotnego zaparcia, w zależności od jego patogenezy i uciążliwości, zaleca się modyfikację stylu życia, farmakoterapię, trening defekacyjny (ang. *biofeedback*) lub leczenie operacyjne [63]. Zarówno zmiana stylu życia, jak i – co sugerują badania głównie na zwierzętach – część leków stosowanych w zaparciu mogą mieć korzystne działanie z punktu widzenia nefrologicznego.

W pierwszym etapie leczenia zaparcia zwykle zaleca się zwiększenie ilości błonnika pokarmowego w diecie do 20–30 g/d [28, 64], choć korzyści można prawdopodobnie odnieść już przy dawce przekraczającej 10 g/d [65]. Jak podsumowano w ostatniej pracy przeglądowej grupy roboczej ERA (ang. *European Renal Nutrition*), liczne badania obserwacyjne wykazały, że spożycie błonnika jest czynnikiem zmniejszającym ryzyko rozwinięcia PChN w populacji ogólnej i chorych na cukrzycę [66]. Mniej pewne jest znaczenie spożycia błonnika w prewencji

wtórnej PChN: choć istnieją doniesienia o spowolnieniu progresji PChN, zmniejszeniu ryzyka incydentów sercowo-naczyniowych i śmiertelności z jakiejkolwiek przyczyny wraz ze wzrostem spożycia błonnika przez chorych z PChN, wyniki prac nie są w pełni spójne [66].

Kolejną rekomendacją wspólną dla niefarmakologicznego leczenia zaparcia oraz postępowania w PChN jest systematyczny wysiłek fizyczny [64, 67]. Choć rzeczywista skuteczność wysiłku fizycznego w leczeniu zaparcia jest niepewna (sposób przeprowadzenia badań wprowadzał duże ryzyko błędu systematycznego), dostępne dowody przemawiają na korzyść ćwiczeń aerobowych [68]. Podobnie w przypadku prewencji pierwotnej PChN: wydaje się, że w porównaniu z osobami o małej aktywności fizycznej osoby o wysokiej aktywności fizycznej rzadziej rozwijają PChN [OR: 0,82 (95% CI: 0,69–0,98); bardzo niskiej jakości dowody] i albuminurię [OR: 0,88 (95% CI: 0,81–0,96); niskiej jakości dowody] [69]. U dorosłych z PChN ćwiczenia aerobowe istotnie poprawiają szczytowe pochłanianie tlenu (ang. *VO_2 peak*), wydłużają czas wysiłku fizycznego, podwyższają stężenie cholesterolu lipoprotein o wysokiej gęstości (HDL-C) i poprawiają HRQoL (w zakresie ogólnego poczucia zdrowia, dolegliwości bólowych oraz ograniczeń w pełnieniu ról z powodu zdrowia fizycznego) [70].

Wstępne dane literaturowe sugerują, że podjęcie farmakologicznego leczenia zaparcia może prowadzić nie tylko do ustąpienia dolegliwości, lecz także do spowolnienia progresji PChN. W oparciu o obserwacje na modelu zwierzęcym PChN indukowanej adeniną, takie właściwości przypisuje się laktulozie oraz dwóm lekom sekrecyjnym: linaklotydowi i lubiprostonowi [71–73]. U gryzoni, które po wyindukowaniu choroby nerek otrzymywały jeden z wyżej wymienionych leków stosowanych w leczeniu zaparcia, obserwowano niższe stężenia kreatyniny, mocznika i wybranych toksyn mocznicowych pochodzenia jelitowego (najczęściej siarczanu indoksylu) w surowicy oraz wykazywano mniejsze nasilenie włóknienia nerek w porównaniu z grupami kontrolnymi [71–73].

Wpływ leków stosowanych w zaparciu na przebieg PChN u ludzi pozostaje w dużej mierze nadal niepoznany. Najwięcej danych dotyczy lubiprostonu. W serii dwóch przypadków pacjentów z nefropatią IgA zaobserwowano w trakcie 12-miesięcznego leczenia zmniejszenie krwinkomoczu, nienerczycowego białkomoczu i wydalania z moczem białka wiążącego kwasy tłuszczowe 1 (ang. *fatty acid-binding protein 1*, FABP1), które interpretowane było jako marker uszkodzenia cewek nerkowych [74]. Pacjenci ci w trakcie obserwacji nie otrzymywali standardowego leczenia zachowawczego, jednak z powodu samoograniczającego się charakteru nefropatii IgA wnioski z doniesienia należy wysuwać ostrożnie. W japońskim, nierandomizowanym badaniu naprzemiennym (ang. *crossover trial*) porównano wpływ lubiprostonu (i omówionego niżej linaklotydu) do sennozydów (grupa substancji czynnych pochodzenia roślinnego o właściwościach przeczyszczających) u 25 hemodializowanych pacjentów z przewlekłym zaparciem. W trakcie miesięcznej terapii lubiprostonem zaobserwowano potencjalnie korzystne zmiany u pacjentów z niecukrzycową chorobą nerek: istotny statystycznie spadek surowiczego stężenia nieorganicznych fosforanów ($4,5 \pm 1,4 \rightarrow 3,8 \pm 1,0$ mg/dl, $P = 0,004$) i kreatyniny ($6,3 \pm 2,45 \rightarrow 5,9 \pm 2,2$ mg/dl, $P = 0,04$) [75]. U pacjentów z cukrzycową chorobą nerek nie zaobserwowano żadnych zmian w zakresie stężeń kreatyniny, azotu mocznika, Na, K, Ca, Pi, Cl i albuminy w surowicy. Skuteczność lubiprostonu w obu grupach w zakresie redukcji objawów zaparcia była nie mniejsza niż sennozydów (analiza typu *non-inferiority*) [75]. W pozostałych dwóch niewielkich japońskich badaniach obserwacyjnych również odnotowano spadek stężenia nieorganicznych fosforanów w surowicy po leczeniu lubiprostonem w trakcie 3-miesięcznej obserwacji 28 pacjentów hemodializowanych ($4,7 \pm 1,5 \rightarrow 3,8 \pm 1,1$ mg/dl, $P < 0,001$ [76]) oraz w trakcie 2-tygodniowej obserwacji siedmiu pacjentów hemodializowanych ($5,8 \pm 0,9 \rightarrow 5,1 \pm 0,8$ mg/dl, $P = 0,03$ [77]). W obu badaniach nie stwierdzono istotnych zmian w stężeniach Na, Cl, K, Ca po leczeniu lubiprostonem [76, 77]. Jak opisano, choć wskazuje się na korzystne działanie lubiprostonu

u pacjentów z PChN, przesłanki te pochodzą z nieusystematyzowanych obserwacji klinicznych i badań obciążonych wysokim ryzykiem błędu systematycznego. Wymagają one weryfikacji w randomizowanych, podwójnie zaślepionych, kontrolowanych badaniach klinicznych.

Kolejnym lekiem stosowanym w zaparciu, w przypadku którego bada się potencjalne właściwości nefroprotekcyjnych, jest laktuloza. O ile właściwości prebiotyczne laktulozy u ludzi zostały dość dobrze opisane, o tyle jej wpływ na stężenia toksyn mocznicowych pochodzenia jelitowego pozostaje niepewny, gdyż dostępna jest jedynie niewielka liczba badań przeprowadzonych głównie wśród osób zdrowych [78]. Autorzy niewielkiego, randomizowanego badania klinicznego testującego wpływ 8-tygodniowej podaży laktulozy u pacjentów z PChN w stadium G3 i G4 stwierdzili redukcję stężenia kreatyniny w surowicy oraz wzrost liczby bakterii należących do rodzajów *Lactobacillus* i *Bifidobacterium* w kale [79]. Do rezultatów należy jednak podchodzić z dystansem nie tylko z powodu małej liczebności grup (po 16 osób) i użytych metod analitycznych, lecz także dużej dawki laktulozy (3 × 20 g), która zdaniem autorów nie wywoływała u pacjentów działań niepożądanych.

Spośród leków omawianych w niniejszym podrozdziale najmniej danych o wpływie na przebieg PChN u ludzi dostępnych jest na temat linaklotydu. W przytoczonej wcześniej japońskiej pracy porównującej wpływ linaklotydu (i lubiprostonu) do sennozydów u pacjentów hemodializowanych z przewlekłym zaparciem wykazano, że o ile u pacjentów z cukrzycową chorobą nerek nie obserwowano istotnych różnic w zakresie parametrów biochemicznych przed i po miesięcznej terapii linaklotydem (w zakresie stężeń kreatyniny, azotu mocznika, Na, K, Ca, Pi, Cl i albuminy w surowicy), potencjalnie niekorzystne zmiany zaobserwowano u chorych z niecukrzycową chorobą nerek: wystąpił istotny statystycznie wzrost surowiczego stężenia azotu mocznika (61,5 ± 14,4 → 70,3 ± 16,2 mg/dl, $P = 0{,}005$) i potasu (4,5 ± 0,6 → 5,2 ± 0,8 mmol/l, $P < 0.001$) [75]. Należy jednak zaznaczyć, że miesięczna terapia linaklotydem prowadziła do istotnej redukcji dolegliwości (głównie w zakresie poczucia kompletności

wypróżnienia) jedynie u chorych z niecukrzycową chorobą nerek; skuteczność linaklotydu u hemodializowanych z cukrzycową chorobą nerek została określona jako nie mniejsza w porównaniu z sennozydami (analiza typu *non-inferiority*) [75].

Podsumowując, wdrożenie rekomendowanego postępowania niefarmakologicznego i farmakologicznego może przynieść korzyści przekraczające lepszą kontrolę dolegliwości pacjentów. Poza wymienionymi wyżej korzyściami sugerowanymi w badaniach na modelach zwierzęcych, badaniach obserwacyjnych i pojedynczych badaniach klinicznych, w swojej pracy przeglądowej z 2019 roku profesorowie K. Sumida i C.P. Kovesdy w oparciu o odkrycia dotyczące tak zwanej osi jelito-nerka-serce wysunęli hipotezę, że wdrożenie leków stosowanych w zaparciu może redukować ryzyko sercowo-naczyniowe u pacjentów z PChN [80].

Aby lekarz mógł zarekomendować odpowiednie postępowanie, niezbędne jest jednak rozpoznanie problemu. Dotychczasowe badania różnych populacji pacjentów wykazały, że rzadko informują oni swoich lekarzy o dolegliwościach z przewodu pokarmowego [22, 81–84]. Co więcej, jak wykazano w przeglądzie systematycznym wchodzącym w skład niniejszej dysertacji (publikacja 3), również część kwestionariuszy używanych do oceny objawów u pacjentów z PChN nie uwzględnia objawów z dolnego odcinka przewodu pokarmowego.

2. Cele pracy

Badanie przekrojowe (publikacja 1.: J. Ruszkowski, Z. Heleniak, E. Król i wsp.: *Constipation and the quality of life in conservatively treated chronic kidney disease patients: a cross-sectional study* [85]; publikacja 2.: J. Ruszkowski, Z. Heleniak, E. Król i wsp.: *Associations between symptoms of constipation and sleep quality in patients with nondialysis chronic kidney disease: a cross sectional study* [86]):

- określenie rozpowszechnienia zaparcia i związanych z nim objawów wśród niedializowanych pacjentów z PChN;
- identyfikacja czynników związanych ze zróżnicowanym rozpowszechnieniem zaparcia i związanych z nim objawów u niedializowanych pacjentów z PChN;
- weryfikacja związku między występowaniem zaparcia i związanych z nim objawów a jakością życia i snu u niedializowanych pacjentów z PChN.

Przegląd systematyczny (publikacja 3.: J. Ruszkowski, K. Majkutewicz, Z. Heleniak i wsp.: *Prevalence and Severity of Lower Gastrointestinal Symptoms amongst Non-Dialysis Chronic Kidney Disease Patients: A Systematic Review and Meta-Analysis* [87]):

- oszacowanie rozpowszechnienia i ciężkości objawów z dolnego odcinka przewodu pokarmowego u niedializowanych pacjentów z PChN na świecie;
- identyfikacja związków między występowaniem lub ciężkością objawów z dolnego odcinka przewodu pokarmowego a HRQoL, wynikami testów laboratoryjnych lub danymi klinicznymi.

3. Materiał i metody

Szczegółowy opis materiału i metod wykorzystanych w badaniach składających się na niniejszą rozprawę doktorską został przedstawiony w opublikowanych artykułach i dołączonych do nich materiałach dodatkowych. Na przeprowadzenie badania, którego wyniki opisano w artykułach 1 i 2, uzyskano zgodę Niezależnej Komisji Bioetycznej przy Gdańskim Uniwersytecie Medycznym (nr zgody: NKBBN/426-56/2018).

3.1. Badanie przekrojowe (publikacje 1-2 [85, 86])

Do przekrojowego badania kwestionariuszowego rekrutowano pełnoletnich pacjentów z PChN zgłaszających się na rutynową wizytę w Poradni Nefrologicznej Uniwersyteckiego Centrum Klinicznego w Gdańsku. Do kryteriów wykluczających z badania przyjęto: bieżące lub przeszłe leczenie nerkozastępcze (metodą dializoterapii lub przeszczepienia nerki), deficyty poznawcze lub zaburzenia widzenia uniemożliwiające wypełnienie kwestionariusza ankiety, ciężkie choroby w trakcie krótkoterminowego intensywnego leczenia. Spośród 111 zrekrutowanych pacjentów 100 wypełniło kwestionariusz ankiety w całości, co umożliwiło dodatkową analizę jakości snu u tych chorych (publikacja 2).

Pacjenci dobrowolnie wypełnili kwestionariusz składający się z następujących części:

- ocena jakości życia związanej ze zdrowiem – polska wersja kwestionariusza SF-36v2 (SF-36v2® Health Survey);
- ocena występowania i nasilenia objawów związanych z zaparciem – polska wersja kwestionariusza PAC-SYM (ang. *Patient Assessment of Constipation-Symptoms*);
- ocena występowania objawów zaparcia czynnościowego – Kryteria Rzymskie III;
- ocena najczęściej występującej konsystencji stolca oraz częstości wypróżnień – bristolska skala uformowania stolca (BSFS) oraz pytanie o średnią liczbę wypróżnień na tydzień;

- ocena jakości snu – polska wersja MOS-Sleep-R (ang. *The Medical Outcomes Study 12-item Sleep Scale-Revised*).

Polskich wersji kwestionariuszy SF-36v2 i MOS-Sleep-R używano po zawarciu niekomercyjnej umowy licencyjnej z OptumInsight Life Sciences, Inc (numer licencji: QM044526). Punktacja obu kwestionariuszy oraz walidacja SF-36v2 została przeprowadzona za pomocą oprogramowania PRO CoRE w wersji 1.4 zapewnionego przez firmę Optum. Polskiej wersji kwestionariusza PAC-SYM używano po zawarciu niekomercyjnej umowy licencyjnej z Mapi Research Trust (numer licencji: 10328).

Z użyciem statystyk opisowych określono częstość występowania poszczególnych objawów z dolnego odcinka przewodu pokarmowego u badanych pacjentów. Związki między występowaniem objawów a danymi demograficznymi, farmakoterapią i współchorobowością weryfikowano z użyciem zmodyfikowanej regresji Poissona (metoda G. Zou'a [88] zgodnie z wytycznymi z 2019 roku [89]). Zależności między występowaniem objawów z przewodu pokarmowego a oceną poszczególnych domen HRQoL oceniano w jedno- i wieloczynnikowych analizach regresji liniowej. Zależności między występowaniem objawów z przewodu pokarmowego a niską jakością snu oceniano z użyciem wspomnianej wyżej zmodyfikowanej regresji Poissona.

Normalność rozkładów zmiennych ciągłych sprawdzano za pomocą testu Shapiro-Wilka. Grupy pacjentów były porównywane za pomocą odpowiednich testów statystycznych, w tym testu *U* Manna-Whitneya, *H* Kruskala-Wallisa i niezależności chi-kwadrat Pearsona. Siłę korelacji między parametrami ocenianymi w MOS-Sleep-R a skalami PAC-SYM określono za pomocą współczynnika tau (τ) B Kendalla oraz współczynnika korelacji rang rho (ρ) Spearmana. Zależność między funkcją filtracyjną nerek (kategorie wg tercylów eGFR: ≤ 32, 33-43, ≥ 44 ml/min/1,73 m^2) a nasileniem objawów z przewodu pokarmowego oceniono za pomocą współczynnika gamma (γ) Goodmana i Kruskala.

Analizę statystyczną przeprowadzono w oprogramowaniu Statistica v.13.0 (StatSoft Polska) oraz przy pomocy funkcji zaimplementowanych w następujących bibliotekach języka programowania Python: *Pandas*, *Pingouin*, *Statsmodels*. Wartości $p < 0,05$ były uznawane za statystycznie istotne. W przypadku porównań wielokrotnych używano poprawki Hommela.

3.2. Przegląd systematyczny (publikacja 3 [87])

Przegląd przygotowano zgodnie z uznaną na świecie metodyką, w oparciu o uprzednio przygotowany protokół zarejestrowany pod numerem CRD42021255122 w Międzynarodowym Prospektywnym Rejestrze Przeglądów Systematycznych (PROSPERO, ang. *International Prospective Register of Systematic Reviews*). Wyniki pracy opisano w oparciu o wytyczne PRISMA 2020 [90].

Kryteria włączenia i wyłączenia badań do przeglądu przedstawiono w tabeli 2. W pracy wchodzącej w skład dysertacji nie uwzględniono danych z badań analizujących symptomatologię u pacjentów po przeszczepieniu nerki; wyniki zostaną przedstawione w osobnej pracy.

Tabela 2. Kryteria włączenia i wyłączenia zastosowane w przeglądzie systematycznym.

Kategoria	**Kryteria włączenia**	**Kryteria wyłączenia**
Populacja	• dorośli (wiek ≥ 18 lat) z rozpoznaną PChN	• kobiety ciężarne; • pacjenci poddawani dializoterapii.
Kontekst	• opieka ambulatoryjna lub pozostawanie bez opieki medycznej; • dowolna lokalizacja geograficzna przeprowadzenia badania.	• hospitalizacja (obecność w placówce świadczącej usługi medyczne dłużej niż jeden dzień); • leczenie stanów ostrych.

Tabela 2 (c.d.). Kryteria włączenia i wyłączenia zastosowane w przeglądzie systematycznym.

Przedmiot zainteresowania	• rozpowszechnienie i nasilenie rozpoznanych samodzielnie przez pacjenta: o biegunki, o bólu brzucha, o bólu odbytu, o nietrzymania stolca, o wzdęcia brzucha, o zaparcia. • rozpowszechnienie: o biegunki czynnościowej, o wzdęcia czynnościowego, o zaparcia czynnościowego, o czynnościowego bólu odbytu i odbytnicy, o zespołu bólu brzucha ośrodkowo-zależnego, o typów konsystencji stolca według BSFS (typy 1-2, 3-5, 6-7), o kategorii częstości wypróżnień (< 3, < 7, 7, lub > 7 wypróżnień/tydzień). • zależności między każdym z wyżej wymienionych objawów/zespołów objawów/parametrów z dolnego odcinka przewodu pokarmowego a: o HRQoL, o wynikami badań laboratoryjnych, o danymi klinicznymi.	• wskaźniki zastępcze (ang. *proxy indicators*) świadczące o występowaniu objawów (np. używanie środków przeczyszczających jako odpowiednik występowania zaparcia) • dostępne dane tylko o złożonych punktach*
Typ badania/publikacji	• badania obserwacyjne; • przekrojowa analiza pacjentów włączonych do randomizowanych badań klinicznych (stan przed interwencją) w przypadku rekrutacji niezależnej od obecności objawów z przewodu pokarmowego.	• artykuły wstępne, • biografie, • metaanalizy, • opisy przypadków, • prace przeglądowe, • protokoły badań, • randomizowane kontrolowane badania kliniczne.

* Przykładami takich złożonych parametrów są skale kwestionariusza *Gastrointestinal Symptom Rating Scale* (np. na skalę "ból brzucha" składają się pytania o następujące objawy: (1) ból/dyskomfort w nadbrzuszu, (2) bóle głodowe żołądka, (3) nudności).

Zastosowano szeroką strategię wyszukiwania źródeł danych. Przeszukane zostały: MEDLINE (poprzez PubMed), Scopus, Web of Science Core Collection, Korean Journal Database (poprzez Web of Science), SciELO (poprzez Web of Science) i Open Dissertations (poprzez EBSCO). Ostatnie przeszukanie baz wykonano 27 listopada 2021. Selekcji poddane zostały także streszczenia konferencyjne *ASN Kidney Week* z lat 2011–2021 (głównej międzynarodowej konferencji nefrologicznej organizowanej przez *American Society of Nephrology*). Strategie wyszukiwania zostały starannie przygotowane w oparciu o:

- walidowany wysokoczuły filtr wyszukiwania badań dotyczących PChN [91];
- hasła przedmiotowe *Medical Subject Headings* (MeSH), słowa kluczowe i ich synonimy dotyczące objawów z dolnego odcinka przewodu pokarmowego;
- filtr odsiewający badania z wykorzystaniem jedynie zwierząt lub osób niepełnoletnich;
- filtr odsiewający badania o niewłaściwym schemacie badawczym (np. opis przypadku) i publikacje niewłaściwego typu (np. prace poglądowe).

Wszystkie strategie przedstawiono w tabeli S2 w materiałach dodatkowych do opublikowanego artykułu [87]. Dodatkowo za pomocą aplikacji sieciowej *CitationChaser* (https://estech.shinyapps.io/citationchaser/) uzyskano bazę cytowań 18 kwestionariuszy służących do oceny objawów (listę kwestionariuszy przedstawiono w tabeli S3 w materiałach dodatkowych do opublikowanego artykułu [87]). Za pomocą tej samej aplikacji 22 stycznia 2022 pobrano wyciąg publikacji cytowanych i cytujących włączone do przeglądu artykuły naukowe.

Po usunięciu duplikatów, tytuły i streszczenia wszystkich rekordów uzyskanych w ramach przeszukiwania baz oraz analizy referencji zostały przeanalizowane niezależnie przez dwie osoby pod kątem kryteriów włączenia i wyłączenia. Następnie uzyskano wersje

pełnotekstowe wstępnie zakwalifikowanych artykułów i poddano je ponownej ocenie kwalifikowalności. Dane z ostatecznie włączonych do przeglądu artykułów zostały pozyskane niezależnie przez dwie osoby za pomocą wcześniej przygotowanego formularza w aplikacji sieciowej *Systematic Review Data Repository Plus* (SRDR+; https://srdrplus.ahrq.gov). Ryzyko błędu systematycznego włączonych badań oceniono za pomocą *Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Prevalence Studies* [92]. W przypadku braku istotnych informacji we włączonych artykułach podjęto próbę kontaktu z autorami prac.

Jeżeli dane na temat rozpowszechnienia lub nasilenia pochodziły z przynajmniej dwóch badań, poddano je jednoetapowej metaanalizie z użyciem uogólnionych liniowych modeli mieszanych (GLMM, ang. *generalized linear mixed models*) lub dwuetapowej metaanalizie po zastosowaniu transformacji Freemana–Tukeya. Do analizy danych, analizy wrażliwości i wykonania rycin użyto języka programowania R, w tym następujących bibliotek: *altmeta*, *DescTools*, *meta*, *metasens*, a także rozszerzenia *MetaXL* do programu *Microsoft Excel*.

4. Omówienie wyników

Rozprawa doktorska została przedstawiona w trzech pracach opublikowanych w recenzowanych czasopismach naukowych notowanych w bazie Journal Citation Report. Poniżej przedstawiono główne wyniki przeprowadzonych badań.

4.1. Badanie przekrojowe (publikacje 1-2 [85, 86])

Charakterystyka zrekrutowanych pacjentów została zaprezentowana w pierwszej tabeli każdej z publikacji (publikacja 1 przedstawia statystyki opisowe dla grupy 111 pacjentów [85], a publikacja 2 statystyki dla podgrupy 100 pacjentów [86]). Jak przedstawiono w publikacji nr 1 [85], do najczęściej zgłaszanych objawów z dolnego odcinka przewodu pokarmowego u ankietowanych pacjentów z PChN należały: wzdęcie (50,9%), napinanie się i wysiłek w celu wypróżnienia (42,7%), zbyt twardy stolec (39,1%), dyskomfort w brzuchu (37,3%), poczucie niezupełnego wypróżnienia (34,5%) i ból brzucha (28,2%). Jeżeli jakikolwiek objaw był obecny, oceniany był przez pacjentów jako łagodny, umiarkowany, ciężki lub bardzo ciężki w kolejno 56,5%, 35,5%, 6,4% i 1,6% przypadków. Dla czterech objawów wykazano istotną zależność między ich nasileniem a funkcją filtracyjną nerek (publikacja 1: tabela 2); były to: bolesne wypróżnienie ($\gamma = -0{,}57$), napinanie się i wysiłek w celu wypróżnienia ($\gamma = -0{,}43$), poczucie niepełnego wypróżnienia ($\gamma = -0{,}37$) i zbyt twardy stolec ($\gamma = -0{,}32$). Wykazano, że u pacjentów z PChN dyskomfort w brzuchu był niezależnie związany z gorszą oceną wszystkich ocenianych domen HRQoL (publikacja 1: tabele 4, S5-S10) i większym rozpowszechnieniem obniżonej jakości snu (publikacja 2: tabele 5, S2, S5). Podobne zależności wykazano dla bólu brzucha (poza brakiem istotnie gorszej oceny jednej z domen HRQoL: wpływu stanu emocjonalnego na życie codzienne).

Twarda konsystencja stolca (typ 1–2 w BSFS) występowała u 28,9% badanych. Wykazano (publikacja 1: tabela 3), że przyjmowanie diuretyków było niezależnym czynnikiem zwiększającym występowanie twardego stolca (skorygowany współczynnik prewalencji,

PR: 2,86, 95% CI: 1,28–6,37, *P* = 0,01). Do pozostałych istotnych niezależnych czynników należała płeć żeńska oraz wiek. Zgłaszanie twardej konsystencji stolca nie było istotnie związane z gorszą oceną HRQoL (publikacja 1) ani jakości snu (publikacja 2).

Zaparcie czynnościowe stwierdzono u 18,9% badanych. Wykazano (publikacja 1: tabela S3), że przyjmowanie paracetamolu było niezależnym czynnikiem związanym z częstszym występowaniem zaparcia czynnościowego [skorygowany PR: 2,67 (95% CI: 1,07–6,64); *P* = 0,035], natomiast przyjmowanie niesteroidowych leków przeciwzapalnych – czynnikiem związanym z mniejszym rozpowszechnieniem zaparcia czynnościowego [skorygowane PR: 0,34 (95% CI 0,11–1,00); *P* = 0,049]. Do pozostałych istotnych niezależnych czynników należała niska wartość eGFR. Stwierdzenie zaparcia czynnościowego było istotnie związane z gorszą oceną HRQoL w zakresie wpływu funkcjonowania fizycznego na życie codzienne (publikacja 1: tabela S6; skorygowane *B* = −19,4; *P* = 0,006), dolegliwości bólowych (publikacja 1: tabela S7; skorygowane *B* = −16,2; *P* = 0,02) oraz witalności (publikacja 1: tabela S8; skorygowane *B* = −10,3; *P* = 0,048). Chorzy z zaparciem czynnościowym gorzej oceniali swoją jakość snu [publikacja 2: tabela 4; estymator Hodgesa–Lehmanna: −7,02 (95% CI: −11,23 do −2,8), *P* = 0,004] i bardziej uskarżali się na zaburzenia inicjacji lub podtrzymania snu [publikacja 2: tabela 4; estymator Hodgesa–Lehmanna: −5,0 (95% CI: −9,99 do −2,49), *P* = 0,003] w porównaniu z pacjentami bez tego zaburzenia. Zaparcie czynnościowe było niezależnym czynnikiem (po uwzględnieniu wieku ≥ 65 lat, depresji, przyjmowania blokerów kanału wapniowego i diuretyków) większego rozpowszechnienia niskiej jakości snu [publikacja 2: tabela 6; skorygowany PR: 2,96 (95% CI: 1,36–6,43), *P* = 0,006] u pacjentów z PChN.

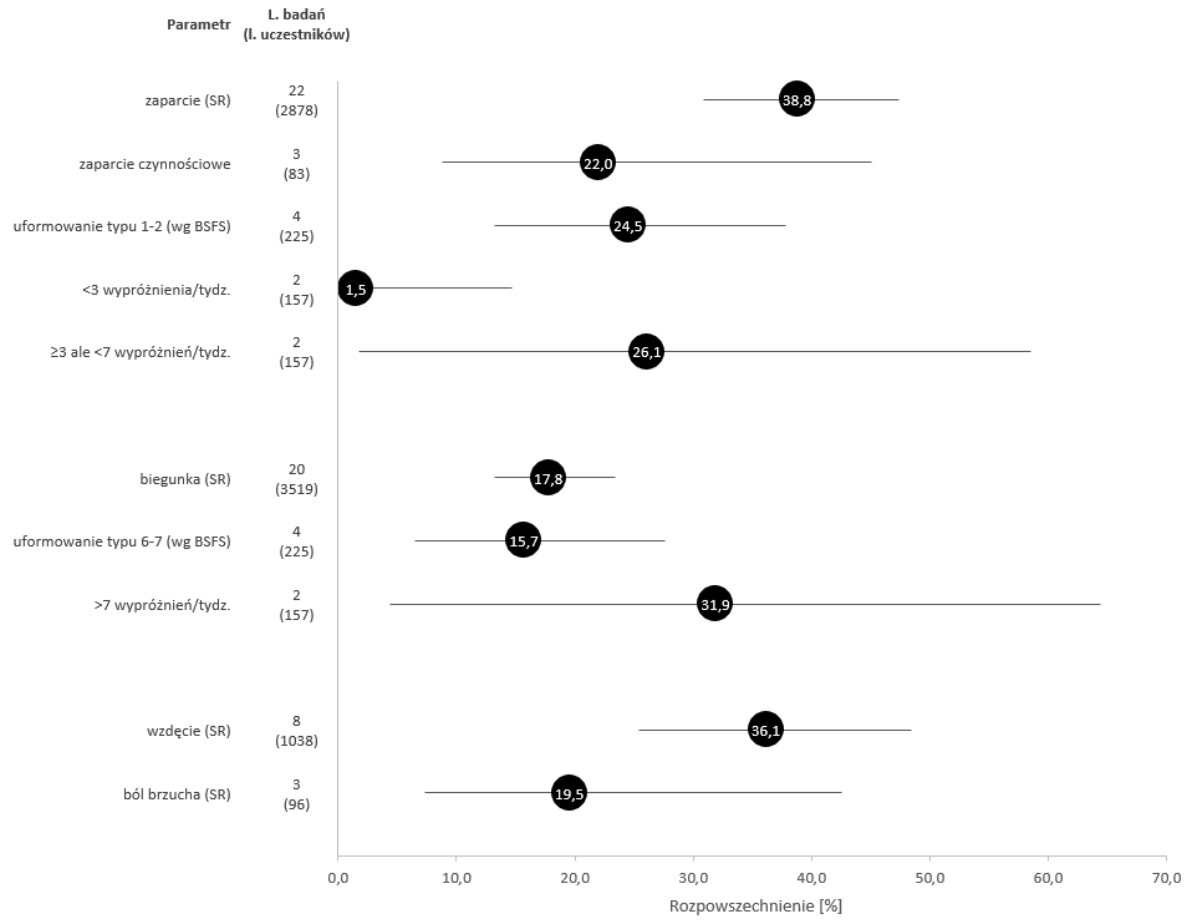
Wypróżnianie rzadziej niż raz dziennie zgłaszało 35,8% ankietowanych pacjentów. Nie udało się zidentyfikować żadnej grupy leków jako niezależnego czynnika zróżnicowanego rozpowszechnienia wypróżniania rzadziej niż raz dziennie (publikacja 1). Wykazano, że

w porównaniu z pacjentami wypróżniającymi się raz dziennie, chorzy wypróżniający się rzadziej gorzej oceniali swoją HRQoL w zakresie funkcjonowania fizycznego (publikacja 1: tabela S5; skorygowane $B = -19{,}3$; $P < 0{,}001$), wpływu funkcjonowania fizycznego na życie codzienne (publikacja 1: tabela S6; skorygowane $B = -20{,}5$; $P < 0{,}001$) i zdrowia psychicznego (publikacja 1: tabela S4; skorygowane $B = -15{,}4$; $P < 0{,}001$). Pacjenci wypróżniający się rzadziej niż raz dziennie, poza problemami z jakością, inicjacją i podtrzymaniem snu (nasilonymi podobnie jak w grupie pacjentów z zaparciem czynnościowym), zgłaszali również gorszą adekwatność snu [publikacja 2: tabela 4; estymator Hodgesa–Lehmanna: −4,9 (95% CI: −9,69 do −4,84), $P < 0{,}001$] i większą senność za dnia [publikacja 2: tabela 4; estymator Hodgesa–Lehmanna: −7,7 (95% CI: −7,72 do −3,85), $P = 0{,}009$]. Wypróżnianie rzadziej niż raz dziennie było niezależnym czynnikiem (po uwzględnieniu wieku ≥ 65 lat, depresji, przyjmowania blokerów kanału wapniowego i diuretyków) większego rozpowszechnienia niskiej jakości snu [publikacja 2: tabela 5; skorygowany PR: 4,64 (95% CI: 1,13–18,97), $P = 0{,}03$] u pacjentów z PChN.

4.2. Przegląd systematyczny (publikacja 3 [87])

W rezultacie kompleksowej strategii wyszukiwania do przeglądu systematycznego [87] włączono 37 badań opisanych w 47 tekstach źródłowych. Dominującym typem były badania przekrojowe (81%). Najwięcej danych pochodziło z dwóch regionów WHO: Regionu Zachodniego Pacyfiku (Australia, Brunei, Chiny, Japonia, Korea Południowa, Malezja) i Regionu Europejskiego (Belgia, Dania, Hiszpania, Holandia, Niemcy, Polska, Szwecja, Turcja, Wielka Brytania, Włochy). W publikacji wskazano na ograniczenia włączonych badań, które mogą skutkować podwyższonym ryzykiem obarczenia uzyskanych wyników błędem systematycznym (m.in. zbyt szerokie kryteria wykluczenia, nielosowy wybór próby badanej).

Najwięcej pozyskanych danych dotyczyło pacjentów z PChN w stadiach G4–5. Wyniki przeprowadzonych metaanaliz rozpowszechnienia objawów dla tej grupy przedstawiono na rycinie 1. Najczęściej ocenianym i najpowszechniej występującym objawem w tej grupie pacjentów okazało się samodzielnie rozpoznane przez pacjenta zaparcie [średnio u 38,8% (95% CI: 30,9–47,4%) chorych; wyniki poszczególnych badań przedstawiono na rycinie 2 omawianego artykułu].



Rycina 1. Średnie rozpowszechnienie objawów, typów uformowania stolca i kategorii częstości wypróżnień zgodnie z przeprowadzonymi metaanalizami dla pacjentów z przewlekłą chorobą nerek w stadium G4–5. Dane poddane metaanalizie zostały przedstawione na rycinach 2-6 i tabeli 2 i S21 w publikacji 3 [87]. Poziome linie reprezentują 95% CI dla średnich, a oznaczenie „SR" wskazuje na objawy rozpoznawane samodzielnie przez pacjenta (ang. *self-reported*).

W analizie podgrup (publikacja 3: tabela S9) stwierdzono, że zaobserwowane różnice między wynikami pochodzącymi z różnych badań ($\hat{\tau}^2$ = 0,60; I^2 = 76%) mogą być częściowo tłumaczone lokalizacją geograficzną ich przeprowadzenia (P = 0,02); badania pochodzące z Regionu Europejskiego wskazywały na niższe rozpowszechnienie samodzielnie rozpoznanego zaparcia (31,4%; 95% CI: 26,8–36,5%) niż te pochodzące z Regionu Zachodniego Pacyfiku [średnie rozpowszechnienie: 41,4% (95% CI: 32,9–50,3%)] lub Regionu Ameryk [średnie rozpowszechnienie: 38,9% (95% CI: 31,6–46,7%)]. Wśród pacjentów z PChN w stadium G4–5 rozpoznających u siebie zaparcie, co około piąty pacjent podawał co najmniej ciężkie nasilenie objawu (tabela 3; wyniki poszczególnych badań zebrano w tabeli S8 omawianego artykułu).

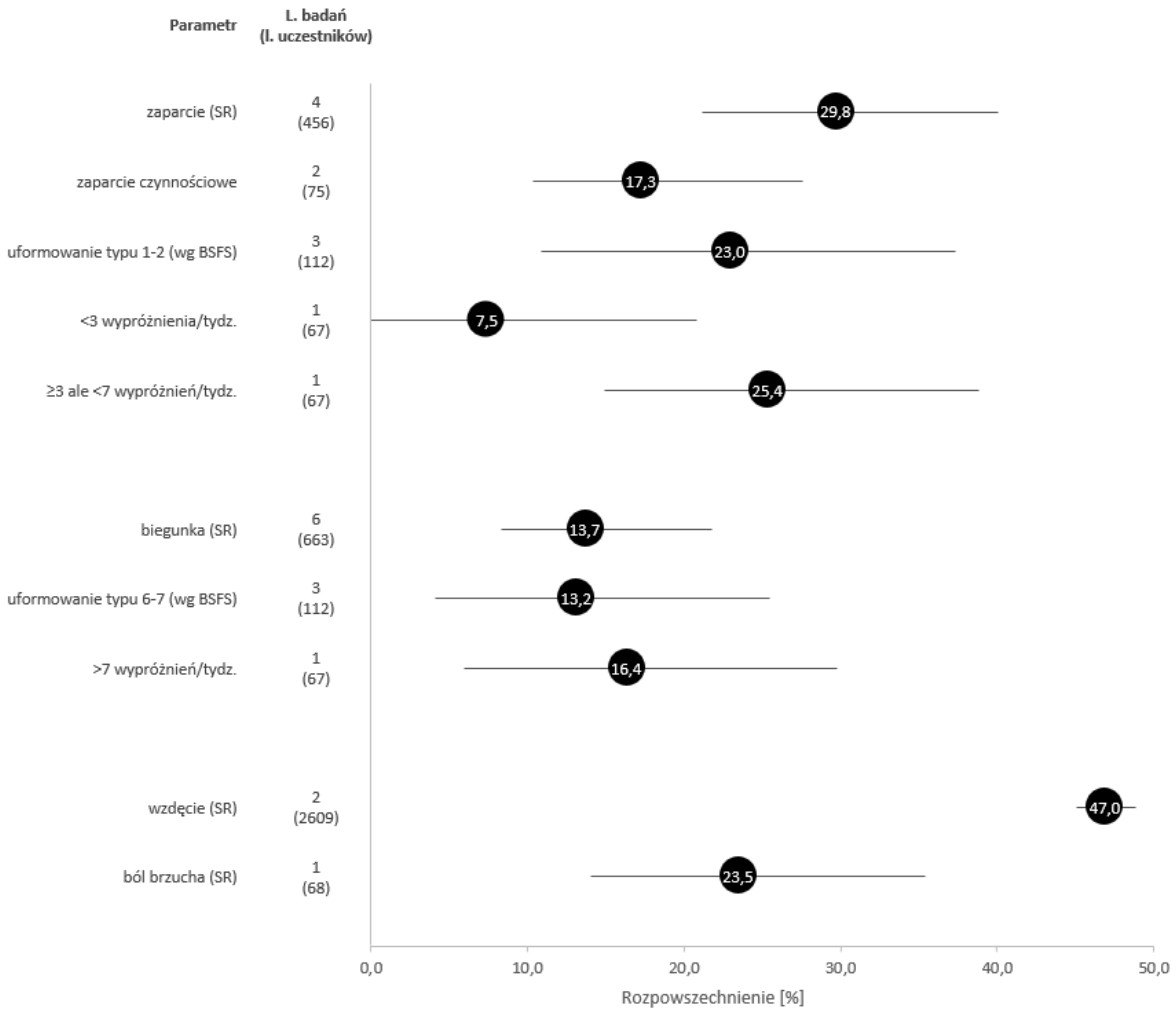
Mniej pozyskanych z literatury danych dotyczyło pacjentów z PChN w stadium G3. Wyniki analiz rozpowszechnienia przedstawiono na rycinie 2. Najczęściej ocenianym objawem w tej grupie pacjentów okazała się samodzielnie rozpoznawana przez nich biegunka [6 badań; średnie rozpowszechnienie: 13,7% (95% CI: 8,4–21,8%); wyniki poszczególnych badań przedstawiono na rycinie 4 omawianego artykułu]. Zwykle była ona postrzegana przez chorych jako łagodny objaw, a jedynie co około dziesiąty podawał co najmniej ciężkie nasilenie dolegliwości (tabela 3; wyniki poszczególnych badań zebrano w tabeli S13 omawianego artykułu). Największe rozpowszechnienie w tej grupie pacjentów oszacowano w przypadku wzdęcia [46,95% (95% CI: 45,0–48,9%)], jednak było ono oceniane jedynie w dwóch badaniach (wyniki poszczególnych badań przedstawiono na rycinie 5 omawianego artykułu).

Tabela 3. Nasilenie objawów u pacjentów z przewlekłą chorobą nerek (pełne wyniki zostały przedstawione w tabelach S8, S13 i S16 publikacji 3).

Samodzielnie rozpoznany objaw	Liczba badań (Liczba uczestników)	Rozpowszechnienie objawu według nasilenia: średnia (95% CI)				Heterogeniczność	
		Łagodny	Umiarkowany	Ciężki	Przytłaczający (bardzo ciężki)	$\hat{\tau}^2$	I^2
Stadia G1–2							
Biegunka [a]	2 (15)	46,8% (15,5-80,9)	20,0% (0-53,9)	13,2% (0-40,2)	20,0% (0-53,9)	0,085	40%
Wzdęcie [b]	1 (10)	80,0% (70-100)	20,0% (10,0-48,7)	0% (0-28,7)	0% (0-28,7)	-	
Zaparcie [b]	1 (7)	57,1% (28,6-91,5)	28,6% (0-62,9)	14,29% (0-48,6)	0% (0-34,3)	-	
Stadium G3							
Biegunka [a]	5 (52)	63,0% (43,7-82,4)	25,2% (9,8-45,4)	8,0% (0-20,9)	3,8% (0-13,6)	0,096	49%
Wzdęcie [b]	1 (30)	50,0% (33,3-68,2)	46,7% (30,0-64,8)	3,3% (0-21,5)	0% (0-18,2)	-	
Zaparcie [a]	3 (108)	37,6% (10,4-69,1)	40,9% (12,8-72,2)	15,8% (0-41,2)	5,7% (0-23,9)	0,182	82%
Stadia G4–5							
Biegunka [a]	10 (205)	47,1% (33,3-59,7)	35,6% (23,0-48,2)	13,5% (5,4-23,6)	3,9% (0,1-10,9)	0,111	68%
Wzdęcie [a]	2 (30)	82,4% (66,6-94,2)		17,6% (5,8-33,4)		0	0
Zaparcie [a]	8 (360)	43,8% (32,8-54,4)	34,4% (24,2-44,9)	18,2% (10,3-27,2)	3,6% (0,4-9,0)	0,064	70%

[a] Wynik dwuetapowej metaanalizy po zastosowaniu transformacji Freemana–Tukeya.

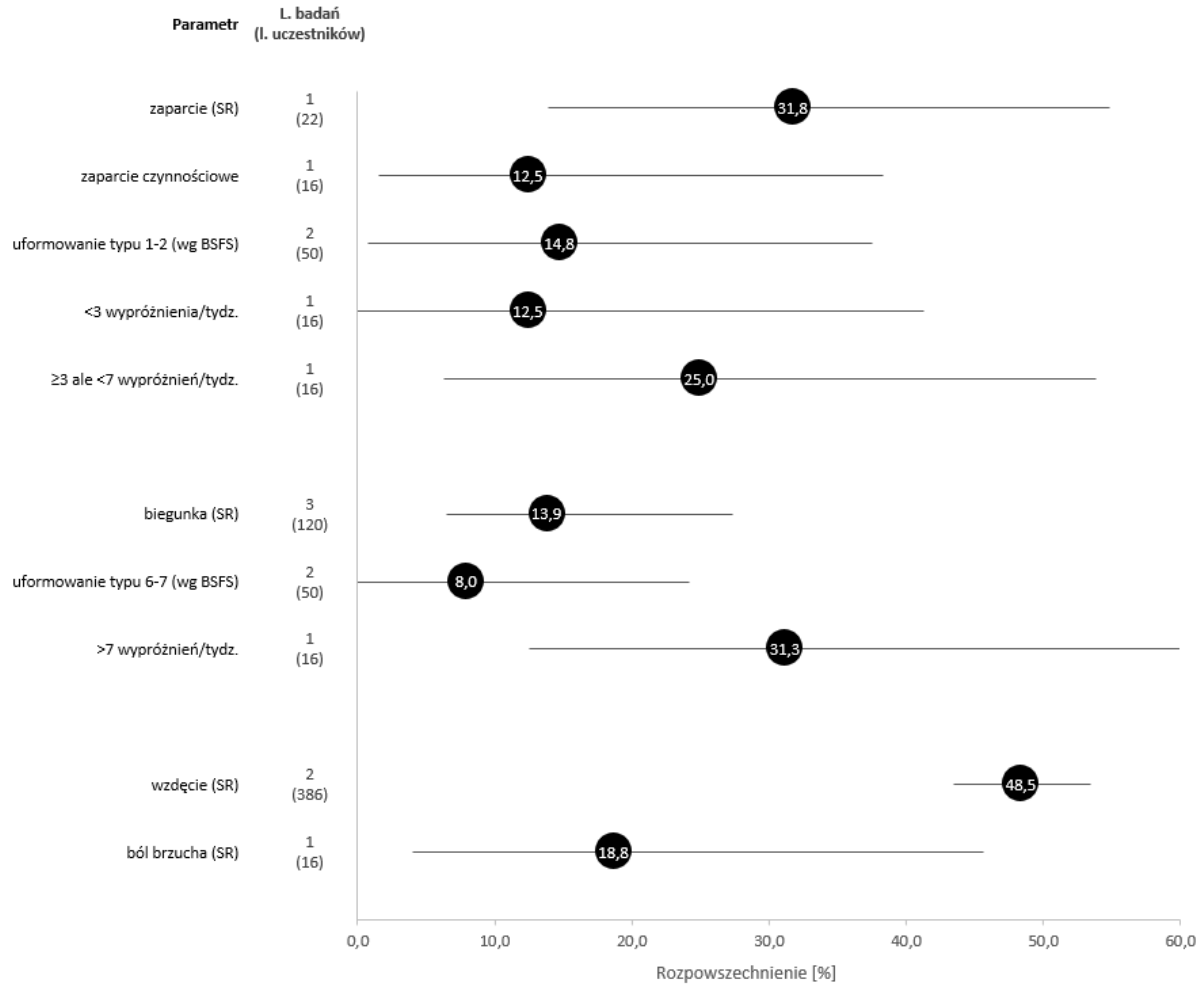
[b] Wobec pochodzenia danych z jednego badania, metaanalizy nie wykonywano; przedziały ufności wyliczono metodą C. P. Sison i J. Glaza.



Rycina 2. Średnie rozpowszechnienie objawów, typów uformowania stolca i kategorii częstości wypróżnień zgodnie z przeprowadzonymi metaanalizami dla pacjentów z przewlekłą chorobą nerek w stadium G3. Dane poddane metaanalizie zostały przedstawione na rycinach 2-6 i tabeli 2 i S21 w publikacji 3 [87]. Poziome linie reprezentują 95% CI dla średnich, a oznaczenie „SR" wskazuje na objawy rozpoznawane samodzielnie przez pacjenta (ang. *self-reported*). W przypadku danych pochodzących z pojedynczych badań, 95% CI wyliczono metodami Cloppera i Pearsona oraz Sisona i Glaza.

Jedynie z sześciu badań pozyskano dane dotyczące pacjentów z PChN w stadiach G1–2. Wyniki analiz zestawiono na rycinie 3. Z powodu małej liczby pacjentów i przeprowadzonych badań, szacowane wartości zarówno rozpowszechnienia, jak i nasilenia objawów (tabela 3) są niepewne, co reprezentują szerokie przedziały ufności. Również w tej grupie pacjentów najczęściej ocenianym objawem była samodzielnie rozpoznawana biegunka

[3 badania; średnie rozpowszechnienie: 13,9% (95% CI: 6,4–27,3%); wyniki poszczególnych badań przedstawiono na rycinie 4 omawianego artykułu]. Największe rozpowszechnienie w tej grupie pacjentów oszacowano w przypadku wzdęcia [48,5% (95% CI: 43,5–53,4%)].



Rycina 3. Średnie rozpowszechnienie objawów, typów uformowania stolca i kategorii częstości wypróżnień zgodnie z przeprowadzonymi metaanalizami dla pacjentów z przewlekłą chorobą nerek w stadium G1. Dane poddane metaanalizie zostały przedstawione na rycinach 2-6 i tabeli 2 i S21 w publikacji 3 [87]. Poziome linie reprezentują 95% CI dla średnich, a oznaczenie „SR" wskazuje na objawy rozpoznawane samodzielnie przez pacjenta (ang. *self-reported*). W przypadku danych pochodzących z pojedynczych badań, 95% CI wyliczono metodami Cloppera i Pearsona oraz Sisona i Glaza.

Dane o związkach między występowaniem lub nasileniem poszczególnych objawów, typami uformowania stolca i częstością wypróżnień a oceną HRQoL oraz danymi klinicznymi i laboratoryjnymi zebrano w siedmiu tabelach dostępnych w materiałach dodatkowych do publikacji 3 (S11, S12, S15, S17, S19, S20, S22). Poniżej wypunktowano główne obserwacje:

1. Nasilenie zaparcia samodzielnie oceniane przez pacjentów korelowało z HRQoL, zarówno w zakresie wymiaru psychicznego, jak i fizycznego, w dwóch badaniach [93, 94].
2. W analizach skupień (ang. *cluster analysis*) przeprowadzonych w dwóch niezależnych badaniach nasilenie biegunki było powiązane z nudnościami i wymiotami [95, 96]. W badaniach tych ani występowanie, ani nasilenie zaparcia nie były powiązane z pozostałymi objawami z przewodu pokarmowego. Do odmiennych wniosków doszli Lee S. J. i wsp., którzy stwierdzili, że zarówno biegunka, jak i zaparcia współwystępowały z "trudnościami ze snem" [97].
3. Czynniki ryzyka i patofizjologia objawów z dolnego odcinka przewodu pokarmowego u pacjentów z PChN były rzadko badane. W dwóch badaniach nie wykazano istotnych różnic w zakresie płci, wieku i BMI między chorymi z zaparciem czynnościowym a pacjentami bez tego zaburzenia [85, 98]. W przypadku biegunki jak dotąd próbowano bezowocnie badać jej związek z neuropatią sercowo-naczyniową [99, 100] oraz sugerowano udział zaburzeń kompozycji kwasów żółciowych [101]. Badanie ankietowe przeprowadzone w ramach doktoratu było jak dotychczas jedynym opublikowanym badaniem oceniającym zależność między farmakoterapią a rozpowszechnieniem szeroko rozumianego zaparcia w PChN (wyniki przytoczono w rozdziale 4.1. niniejszej dysertacji).
4. Konsekwencje kliniczne objawów nie zostały należycie przebadane. W badaniu EQUAL samodzielnie rozpoznane zaparcie było niezależnym predyktorem pogorszenia stanu odżywienia w ciągu 12 miesięcy obserwacji u starszych pacjentów z PChN [102].

5. Dyskusja

5.1. Rozpowszechnienie i nasilenie zaparcia i innych objawów z dolnego odcinka przewodu pokarmowego u niedializowanych pacjentów z przewlekłą chorobą nerek

W niniejszej dysertacji wykazano, że pacjentom z PChN często doskwierają objawy z dolnego odcinka przewodu pokarmowego. Do najbardziej rozpowszechnionych objawów należą rozpoznane samodzielnie przez pacjentów zaparcie i wzdęcie, a także – jak wskazuje badanie przeprowadzone w ośrodku gdańskim – napinanie się i wysiłek w celu wypróżnienia. Nasilenie objawów z dolnego odcinka przewodu pokarmowego w tej populacji chorych było jednak ograniczone; w większości pacjenci oceniali zgłaszane dolegliwości jako łagodne lub umiarkowane. Podsumowane w przeglądzie systematycznym (publikacja 3) wyniki przeprowadzonych dotąd badań należy traktować jednak z rezerwą z powodu częstego problemu z nie w pełni reprezentatywnym charakterem próby dla populacji pacjentów z PChN (zbyt restrykcyjne kryteria włączenia i szerokie kryteria wyłączenia) oraz z powodu nieoptymalnych metod rekrutacji pacjentów (w większości badań: dobór wygodny).

Jak wskazano w załączniku „A" przeglądu systematycznego (publikacja 3), choć w dotychczasowej literaturze rzadko porównywano rozpowszechnienie objawów z przewodu pokarmowego między pacjentami z PChN a populacją ogólną, wydaje się, że rozpowszechnienie analizowanych objawów (rozpoznanego samodzielnie przez pacjenta zaparcia i wzdęcia, a także zaparcia czynnościowego), jest większe u pacjentów z PChN niż w populacji ogólnej. W porównaniu z chorymi dializowanymi pacjenci z zaawansowaną PChN niepoddawani leczeniu nerkozastępczemu charakteryzują się niższą lub porównywalną częstością występowania rozpoznanej samodzielnie biegunki oraz porównywalnym rozpowszechnieniem rozpoznanego samodzielnie zaparcia.

Wysokie rozpowszechnienie objawów (wykazane w publikacjach 1–3) i szerokie możliwości terapeutyczne powinny implikować uwzględnienie dolegliwości z przewodu

pokarmowego w rutynowej ocenie pacjentów z PChN. Niestety wiele kwestionariuszy wykorzystywanych do oceny objawów PChN nie uwzględnia ocenianych w pracy objawów. Biorąc pod uwagę potencjalne nefroprotekcyjne działanie postępowania rekomendowanego w leczeniu zaparcia, niniejsza dysertacja wskazuje na zasadność przeprowadzenia podłużnych (ang. *longitudinal*) badań obserwacyjnych i randomizowanych kontrolowanych badań klinicznych oceniających realne korzyści płynące z podjęcia leczenia zaparcia u pacjentów z PChN.

5.2. Czynniki związane ze zróżnicowanym rozpowszechnieniem objawów z dolnego odcinka przewodu pokarmowego u niedializowanych pacjentów z przewlekłą chorobą nerek

Wśród czynników ryzyka wystąpienia zaparcia w populacji ogólnej wymienia się płeć żeńską, niską aktywność fizyczną, niskie zarobki, miejsce zamieszkania, choroby towarzyszące, przyjmowanie określonych grup leków i spożywanie nieodpowiednich ilości błonnika [103]. W żadnym z badań włączonych do przeglądu systematycznego (publikacja 3) nie stwierdzono, aby płeć istotnie determinowała rozpowszechnienie samodzielnie rozpoznanego zaparcia lub zaparcia czynnościowego u pacjentów z PChN; jedynie w badaniu kwestionariuszowym przeprowadzonym w ramach doktoratu zaobserwowano istotnie większe rozpowszechnienie twardej konsystencji stolca u kobiet niż u mężczyzn. W żadnym z badań włączonych do przeglądu systematycznego nie przedstawiono danych o związku między aktywnością fizyczną lub zarobkami a rozpowszechnieniem samodzielnie rozpoznanego zaparcia, zaparcia czynnościowego lub twardej konsystencji stolca (publikacja 3: tabele S11, S12, S20). Przeprowadzona w ramach metaanalizy analiza podgrup wykazała, że miejsce (region WHO) przeprowadzania badań kwestionariuszowych wiązało się z istotnie różnym rozpowszechnieniem samodzielnie rozpoznanego zaparcia u pacjentów z PChN w stadium G4–5: badania przeprowadzone w Regionie Europejskim podawały niższe rozpowszechnienie objawu niż badania pochodzące z Regionu Zachodniego Pacyfiku lub Regionu Ameryk

(publikacja 3, tabela S9). Jak wykazano w przeglądzie systematycznym, badanie ankietowe przeprowadzone w ramach doktoratu okazało się jedynym podejmującym próbę określenia związku między farmakoterapią pacjentów a występowaniem objawów z przewodu pokarmowego u pacjentów z PChN. Wskazano, że przyjmowanie paracetamolu może być powiązane z większym rozpowszechnieniem zaparcia czynnościowego, a diuretyków – twardszej konsystencji stolca.

Wśród czynników predysponujących do przewlekłej biegunki w populacji ogólnej wymienia się męską płeć, stres psychiczny, dietę bogatą w alkohol, kofeinę, fermentujące oligo-, di- i monosacharydy oraz poliole (FODMAP, ang. *fermentable oligosaccharides, disaccharides, monosaccharides and polyols*; m.in. laktozę, fruktany, galaktany, sztuczne słodziki), przyjmowanie określonych grup leków i suplementów (m.in. preparaty z magnezem, niesteroidowe leki przeciwzapalne, gliptyny, metformina, antybiotyki) oraz choroby towarzyszące (m.in. nadczynność przytarczyc) [104, 105]. Wśród włączonych do przeglądu systematycznego badań tylko jedno oceniało zależność między płcią a rozpowszechnieniem samodzielnie rozpoznanej biegunki: okazała się ona istotnie większa wśród kobiet [106]. Żadne z dotąd przeprowadzonych badań uwzględnionych w przeglądzie systematycznym [87] nie zweryfikowało zależności między stresem psychicznym, dietą, farmakoterapią lub współchorobowością a rozpowszechnieniem samodzielnie rozpoznanej biegunki u pacjentów z PChN.

Patofizjologia objawów pozostaje jednak nadal bardzo słabo poznana. Jak zasugerowano w przeglądzie systematycznym wchodzącym w skład niniejszej dysertacji [87], poza uwzględnieniem klasycznych czynników ryzyka związanych z poszczególnymi objawami z dolnego odcinka przewodu pokarmowego (m.in. płeć, aktywność fizyczna), przyszłe badania powinny uwzględniać również:

- zaburzenia wynikające z PChN, które mogą uczestniczyć w patogenezie dolegliwości (m.in. zaburzenia endokrynne, dysfunkcje autonomicznego układu nerwowego);
- działania niepożądane przyjmowanych leków;
- obciążenie związane z postępowaniem terapeutycznym w PChN (np. ograniczenia płynowe, psychologiczna bariera przed korzystaniem z toalet publicznych w szpitalach u chorych wymagających częstych hospitalizacji)
- zaburzenia mikrobioty jelitowej.

5.3. Związki między występowaniem lub nasileniem objawów z dolnego odcinka przewodu pokarmowego a HRQoL i jakością snu u niedializowanych pacjentów z przewlekłą chorobą nerek

W przeglądzie systematycznym stwierdzono, że spośród analizowanych objawów to rozpoznane samodzielnie przez pacjentów zaparcie było wiązane w dotychczas przeprowadzonych badaniach najbardziej konsekwentnie z niższą HRQoL, zarówno w zakresie wymiaru psychicznego, jak i fizycznego. Przeprowadzone w ramach projektu doktorskiego badanie ankietowe pozwoliło na uszczegółowienie zależności między szerokorozumianym zaparciem a HRQoL. Okazało się, że już pojedyncze objawy towarzyszące zaparciu – zwłaszcza kojarzone z IBS dyskomfort w jamie brzusznej i ból brzucha – wiążą się z globalnie obniżoną HRQoL. Zarówno obecność objawów zaparcia czynnościowego, jak i wypróżnianie rzadsze niż raz dziennie były związane z gorszą oceną HRQoL w pojedynczych domenach (wspólną cechą była gorsza ocena wpływu funkcjonowania fizycznego na życie codzienne) i niższą jakością snu (dla obu grup charakterystyczne było uskarżanie się na zaburzenia inicjacji lub podtrzymania snu). W zestawieniu z danymi literaturowymi profil gorzej ocenianych domen HRQoL w zaparciu czynnościowym wydaje się inny u pacjentów z PChN niż w populacji ogólnej [46]; wymaga to jednak dalszych badań. W kontraście do wyżej

wymienionych obserwacji stwierdzenie twardej konsystencji stolca nie było istotnie związane z gorszą oceną HRQoL ani jakości snu. Nie przeprowadzono dotąd badań, które weryfikowałyby, czy skuteczne leczenie objawowe zaparcia i związanych z nim wymienionych wyżej dolegliwości skutkowałoby poprawą oceny HRQoL u chorych z PChN niewymagających leczenia nerkozastępczego.

W przypadku pozostałych objawów z dolnego odcinka przewodu pokarmowego dowody przemawiające za ich związkiem z niższą oceną HRQoL u pacjentów z PChN są niejednoznaczne (w przypadku samodzielnie rozpoznanej biegunki), pochodzą z pojedynczych badań (ból brzucha, wzdęcie), lub są nieznane (nietrzymanie stolca, ból odbytu).

6. Wnioski i podsumowanie

Dzięki oszacowaniu rozpowszechnienia i nasilenia wybranych objawów z dolnego odcinka przewodu pokarmowego u pacjentów z PChN, niniejsza dysertacja może stanowić punkt wyjścia do dyskusji o istotności tych niesłusznie bagatelizowanych dotąd objawów.

W wyniku zwiększenia wiedzy o symptomatologii, przedstawiciele zawodów medycznych sprawujący opiekę nad pacjentami z PChN mogą aktywnie dopytywać o objawy (lub, jak wnioskowano w publikacji 3, korzystać z kwestionariuszy uwzględniających takie objawy), a w razie ich stwierdzenia podejmować odpowiednie działania terapeutyczne. Jak zaprezentowano w rozdziale 1.4. niniejszej dysertacji, przypuszcza się, że podjęcie postępowania leczniczego może mieć korzystne skutki daleko wykraczające poza łagodzenie dolegliwości.

Poza implikacjami dla praktyki zawodowej, rezultaty badań przeprowadzonych w ramach projektu doktorskiego mogą także stymulować i ukierunkowywać dalszy rozwój nauki. W przygotowanym przeglądzie systematycznym wskazano jednoznacznie na niewystarczającą ilość danych na temat patofizjologii i konsekwencji objawów z dolnego odcinka przewodu pokarmowego u niedializowanych pacjentów z PChN. Co więcej,

zaznaczono w nim nie tylko ograniczenia metodyczne dotychczasowych badań, lecz także zagadnienia wymagające dalszej eksploracji. W konsekwencji niniejsza dysertacja może posłużyć do projektowania właściwie ukierunkowanych, wysokiej jakości badań poszerzających rozumienie mechanizmów patofizjologicznych oraz następstw klinicznych objawów z dolnego odcinka przewodu pokarmowego w PChN.

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8. Publikacje

Publikacja 1

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Research Paper

Constipation and the Quality of Life in Conservatively Treated Chronic Kidney Disease Patients: A Cross-sectional Study

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Abstract

Background: Constipation is a common gastrointestinal disorder that in general population is associated with worse health-related quality of life (HRQoL). The epidemiology of constipation has not been reliably determined in conservatively-treated CKD patients. We aimed to determine the prevalence of constipation and constipation-related symptoms in conservatively-treated CKD patients, to find factors associated with their altered prevalence ratio (PR), and to verify the associations between constipation and HRQoL.

Methods: In this cross-sectional study, 111 conservatively-treated CKD outpatients fulfilled questionnaires that included questions addressing HRQoL (SF-36v2®), constipation-related symptoms (The Patient Assessment of Constipation-Symptoms questionnaire), the Bristol stool form scale (BSFS), Rome III criteria of functional constipation (FC), and frequency of bowel movement (BM).

Results: Depending on the used definition, the prevalence of constipation was 6.6-28.9%. Diuretics and paracetamol were independently associated with increased PR of BSFS-diagnosed constipation (PR 2.86, 95% CI 1.28-6.37, P = 0.01) and FC (PR 2.67, 95% CI 1.07-6.64, P = 0.035), respectively. The most commonly reported symptoms were bloating (50.9%) and straining to pass a BM (42.7%). Abdominal discomfort (37.3%) was independently associated with worse scores in all analyzed HRQoL domains. In multiple regressions, FC and having <7 BM/week, but not BSFS-diagnosed constipation, were associated with lower scores in several HRQoL domains.

Conclusions: Constipation and related symptoms are prevalent in CKD patients. FC and decreased frequency of defecation, but not BSFS-diagnosed constipation, are associated with worse assessment of HRQoL in conservatively-treated CKD patients.

Key words: chronic kidney disease, constipation, flatulence, SF-36v2

Introduction

Constipation is a common gastrointestinal problem. In the general population of Europe, the mean value of the reported constipation prevalence is 17.1%, and its higher value is frequently associated with older age, female sex, less self-reported physical activity, and certain medications [1, 2]. In general population, constipation is associated not only with worse health-related quality of life (HRQoL) [3, 4] but also with higher risk of cardiovascular events and all-cause mortality [5–7].

Chronic kidney disease (CKD), that is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health [8], is a condition affecting approximately 9.1-13.4% of the global population [9, 10]. The severity of CKD is divided into 5 stages (G1-G5) according to the level of

glomerular filtration rate (GFR). Recent studies suggest a two-way relationship between constipation and CKD. On the one hand, the presence of constipation is independently associated with a higher risk of developing CKD and end-stage renal disease (ESRD); it is hypothesized that these relationships can be mediated by an altered gut microbiota and/or be a result of common cause such as lack of regular physical activity [11–13]. On the other hand, CKD since its moderate stage (i.e. G3b, eGFR < 45 ml/min/1.73 m^2) is known to be associated with several upper gastrointestinal symptoms such as loss of appetite and vomiting [14]. As the disease progresses, the prevalence of the gastrointestinal (GI) symptoms increases [14, 15]. Among all GI symptoms, constipation is the most frequently assessed GI symptom in dialysis patients, and the prevalence of constipation is higher in hemodialysis (HD) patient than in peritoneal dialysis (PD) patients (23.8-71.7% vs 14.2-28.9% of patients, respectively) [16]. In dialysis patients, like in a general population, constipation is associated with worse HRQoL [17].

However, there is little known on the epidemiology of constipation and related symptoms in patients in the earlier stages of CKD (non-ESRD) [18]. The present study aimed to determine the prevalence of constipation and constipation-related symptoms in conservatively-treated CKD patients, to find factors associated with their altered prevalence ratio (PR), and to verify the associations between the occurrence of constipation and HRQoL.

Materials and Methods

This cross-sectional study was carried out within the time frame of June 2018 and December 2019. We recruited a total of 111 outpatients that were visiting Nephrological Outpatient Clinic, a part of the University Clinical Centre in Gdańsk. Ethical permission for the study was obtained from the Bioethical Committee for Scientific Research at the Medical University of Gdańsk (NKBBN/426-56/2018).

The participants were selected according to the following criteria: diagnosis of CKD, age above 18 years, voluntary participation. Exclusion criteria were receiving currently or in the past dialysis, kidney transplantation, cognitive deficits and visual impairment that unable of answering the questionnaire; having a serious illness in an acute treatment phase. All patients were informed about the nature and purposes of the study. As the research was based on the voluntarily filled anonymous surveys, additional written informed consents were unnecessary and were not collected.

All included participants were asked to voluntarily complete questionnaires that included a battery of surveys: (1) addressing the HRQoL: the Polish versions of the SF-36v2® Health Survey (SF-36v2); (2) addressing symptoms of constipation: a question about the number of defecation per week, The Patient Assessment of Constipation-Symptoms (PAC-SYM) questionnaire [19], simple questions containing Rome III criteria of functional constipation (FC) [20], and a request to select the most common stool consistency on the Bristol stool form scale (BSFS) [21, 22].

The physician completed a questionnaire that included multiple-choice questions about comorbidities (diabetes, hypertension, heart failure, hypothyroidism, depression, inflammatory bowel disease) and taken medications (iron, calcium, vitamin D, antihistamines, calcium channel blockers, beta-blockers, diuretics, hypnotics, tricyclic antidepressants, nonsteroidal anti-inflammatory drugs, paracetamol, lactulose, other laxatives, probiotics, oral contraceptives). Data on sex, age, body weight, height, estimated glomerular filtration rate (eGFR) based on CKD-EPI formula, and etiology of CKD were collected. The body mass index (BMI) was calculated as the body weight divided by the square of the body height.

To use the SF-36v2, a non-commercial license agreement was made between JR and OptumInsight Life Sciences, Inc. (license number: QM044526). Validation and scoring of SF-36v2 were performed using desktop scoring software PRO CoRE Version 1.4 provided by Optum. The SF-36v2 questionnaire consists of 36 items that measure eight dimensions of HRQoL: physical functioning (PF); role limitations due to physical health problems (RP); bodily pain (BP); general health perception (GH); vitality (VT); social functioning (SF); role limitations due to emotional problems (RE); and mental health (MH). All dimensions are scored such that higher scores indicate better HRQoL. Firstly, the reliability and validity of subscales were tested (Supplementary material, *Table S1*). Only the GH subscale was neither reliable (Cronbach's alpha = 0.65) nor valid. This finding is supported by Żołnierczyk-Zreda who found that all subscales of the Polish version of SF-36v2, besides GH (Cronbach's alpha = 0.63), are reliable in general population [23]. Based on the poor reliability and validity of GH, it was excluded from further analysis.

To use the PAC-SYM, a non-commercial license agreement was made between JR and Mapi Research Trust (license number: 10328). The questionnaire contains 12 items assessing the severity of abdominal, rectal, and stool symptoms of constipation [19]. Items are scored on 5-point Likert scale (0 = "symptom absent", 1 = "mild", 2 = "moderate", 3 = "severe", and

4 = "very severe"). In statistical analysis, due to small number of patients reporting "severe" or "very severe" symptoms, they were counted together with patients reporting "moderate" severity of symptoms.

In the context of BSFS, constipation was defined as either type 1 ("Separate hard lumps, like nuts (difficult to pass)") or type 2 ("Sausage-shaped but lumpy") stool form. For the diagnosis of FC, the presence of at least 2 out of 6 symptoms (straining; lumpy or hard stools; sensation of incomplete evacuation; sensation of anorectal obstruction or blockage during defecation; less than three bowel movements per week; need for manual maneuvers to facilitate defecation) in at least 25% of the defecations, for at least 3 months, with symptom onset at least 6 months before diagnosis, had been met [20].

Statistical analysis

Testing the normality of the distribution of collected data was performed using the Shapiro–Wilk test. Continuous variables with non-normal distribution were presented using medians and interquartile ranges (IQR). Categorical variables were presented as a percentage share of the obtained data. Patient groups were compared using Mann–Whitney *U*, Kruskal–Wallis ANOVA, and Pearson's chi–squared (χ^2) tests. Statistical testing was done with Statistica, v.13.0 (StatSoft Polska, Inc. 2016) and Python libraries: Pandas [24], Pingouin [25], Statsmodels [26]. *P* values < 0.05 were considered significant. *P* values for multiple comparisons were adjusted using Hommel method. Figure 2 was designed in Microsoft Excel 2013.

Due to high disproportion in number of patients across stages of CKD, patients were divided into 3 groups according to eGFR terciles: with low eGFR (≤ 32 ml/min/1.73 m²), medium eGFR (33-43 ml/min/1.73 m²), and high eGFR (≥44 ml/min/1.73 m²). Correlations between eGFR terciles and symptoms severities were presented as Goodman–Kruskal gamma coefficient, and their significance was tested with *Z*-test.

As several variables were suspected to be associated with constipation, we used Poisson regression models with robust variance (computed with Statsmodels adaptation of R code published by Gallis and Turner [27]) to estimate prevalence ratio (PR) simultaneously controlling for multiple variables. Potential predictors of constipation occurrence were age, BMI, sex, eGFR terciles, comorbidities (all besides hypertension as it is not associated with altered gastrointestinal motility in the literature), and taking specific medications. All variables were initially tested in univariate Poisson regression models with robust variance. If *P* value of model testing the association between taking a drug and constipation was lower than 0.20, this variable was selected for inclusion into a single Poisson regression model with all variables related to demographics and comorbidities. If the interaction between sex and age was statistically significant, it was added to the multiple regression model.

To determine whether constipation or constipation-related symptoms were independently associated with altered score in any of the HRQoL domain, multivariable ordinary least squares regressions were applied. Each of the models was adjusted to sex, age, BMI, eGFR tercile and comorbidities. Such models were shown if both GI symptom coefficient significantly differs from zero (*T*-test) and its adding to model significantly improves model (ANOVA *F*-test). To select final model for each HRQoL domain, among models with all combinations of GI symptoms from the previous step, one was chosen based on Akaike's information criterion that aims to balance goodness-of-fit and model complexity.

Results

We have screened 150 patients. The main exclusion criteria were as follows: visual impairment that made it impossible to complete the questionnaire; lack of consent without explaining the reason.

Demographics and comorbidities

Demographics and comorbidities were presented in Table 1. Except for the higher frequency of hypothyroidism in women (26.5% vs men: 8.1%; unadjusted $P = 0.009$, adjusted $P = 0.04$), no other differences were found between sexes. Similarly, patients divided into groups based on terciles of eGFR did not differ between each other in manner of comorbidities nor BMI, but patients with medium eGFR were significantly older than those with high eGFR (adjusted $P = 0.01$; post-hoc $P = 0.005$).

Constipation and related symptoms

The median number of defecation per week was 7 (IQR: 6-7). No differences were found in the frequency of defecation neither between genders nor among eGFR terciles (data not shown). In Figure 1, the distribution of bowel movements (BMs) frequency per week was shown. The majority of patients—43.4%—reported a mean seven BMs a week. Lower frequency of defecation occurred in 35.8% of patients, and 6.6% of patients reported frequency even lower than three BMs a week. In contrast, 20.8% of patients had BM more often than once a day. Interestingly, lower than mean 7 BMs per week was reported by 25.0%, 39.4%, and 43.2% of patients with

high, medium, and low eGFR, but the observed difference was insignificant (P = 0.23).

The most commonly reported symptoms in the PAC-SYM questionnaire were following: bloating (50.9%), straining/squeezing to pass BM (42.7%), too hard stool (39.1%), abdominal discomfort (37.3%), and feeling of incomplete BM (34.5%). If a symptom was reported, it was reported to be mild, moderate, severe and very severe in 56.5%, 35.5%, 6.4% and 1.6% of cases, respectively (see Fig. 2 for absolute numbers). After adjustment for multiple comparisons, patients with high, medium and low eGFR did not significantly differ in the frequency of constipation-related symptoms; however, terciles of eGFR did negatively correlate with severity of four symptoms (Table 2), i.e. patients with lower eGFR more frequently reported higher severity of the symptoms.

FC and constipation diagnosed with BSFS were found in 21 (18.9%) and 28 (28.9% of patients who completed the scale) of patients, respectively. Neither the above-mentioned symptoms nor any kind of constipation were associated with gender (data not shown).

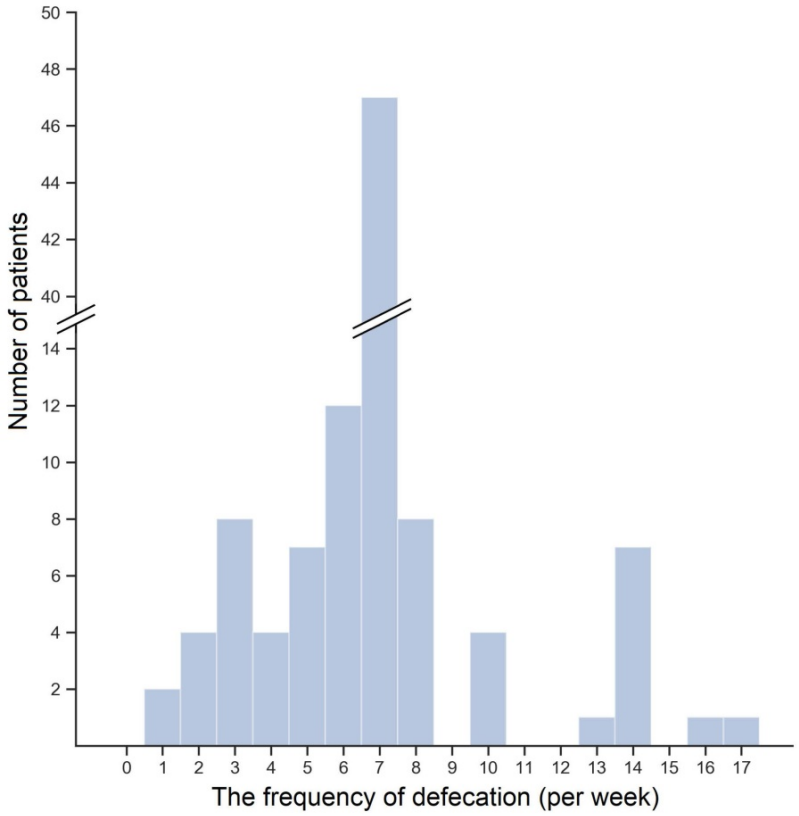

Figure 1. The histogram of the bowel movements frequency per week

Table 1. Demographic and clinical parameters of the total study population and according to eGFR tercile

	All	High eGFR tercile	Medium eGFR tercile	Low eGFR tercile	Unadjusted *P* value
Participants, n	111	37	34	40	-
Male, n (%)	62 (55.9)	21 (56.8)	12 (35.3)	29 (72.5)	0.006
Age, years, median (IQR)	68 (55.0-74.0)	64 (44.0-71.0)	71.0 (68.0-76.0)	66.0 (53.5-72.5)	0.005
BMI, kg/m², median (IQR)	28.48 (25.63-31.14)	28.09 (25.18-30.76)	28.48 (26.23-30.49)	28.58 (24.49-31.92)	0.84
eGFR, median (IQR)	38.0 (30.0-48.0)	57.0 (48.0-67.0)	38.0 (35.0-42.0)	26.5 (17.0-31.0)	<0.001
Hypertension, n (%)	97 (87.4)	31 (83.8)	32 (94.1)	34 (85.0)	0.36
Diabetes, n (%)	35 (31.5)	6 (16.2)	13 (38.2)	16 (40.0)	0.05
Heart failure, n (%)	22 (19.8)	4 (10.8)	8 (23.5)	10 (25.0)	0.24
Hypothyroidism, n (%)	18 (16.2)	6 (16.2)	7 (20.6)	5 (12.5)	0.64
Depression, n (%)	5 (4.5)	0	3 (8.8)	2 (5.0)	0.20

Abbreviations: BMI: body mass index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate

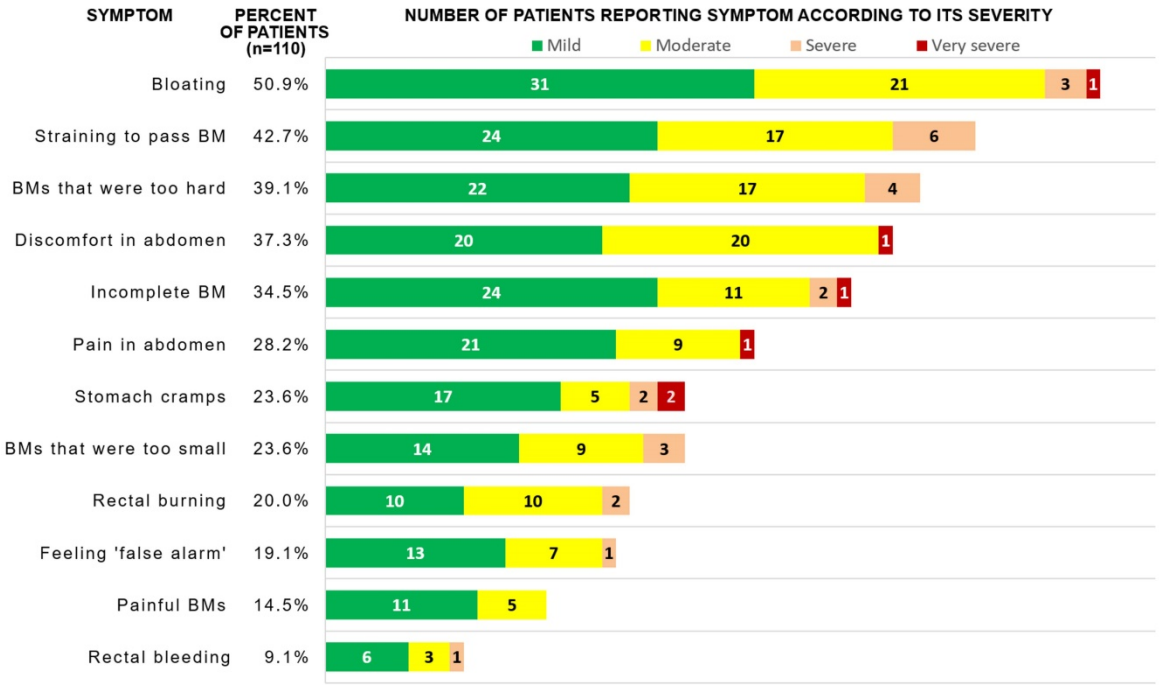

Figure 2. Frequency of symptom reporting and absolute number of patients reporting each severity of gastrointestinal symptoms in PAC-SYM scale

Table 2. The frequencies of constipation-related symptoms reporting by eGFR-grouped patients and the correlations between symptoms severities and eGFR terciles

Symptom and its severity		Percentage of patients reporting the symptom			Gamma coefficient	*P* value	
		High eGFR group (n = 36)	Medium eGFR group (n = 34)	Low eGFR group (n = 40)		Unadjusted	Adjusted
Painful BM	Lack	97.2%	85.3%	75.0%	-0.569	<0.001	0.002
	Mild	0.0%	11.8%	17.5%			
	At least moderate	2.8%	2.9%	7.5%			
Straining to pass BM	Lack	83.3%	82.3%	77.5%	-0.427	<0.001	<0.001
	Mild	11.1%	11.8%	12.5%			
	At least moderate	5.6%	5.9%	10.0%			
Incomplete BM	Lack	75.0%	73.5%	50.0%	-0.371	<0.001	0.006
	Mild	19.4%	17.7%	27.5%			
	At least moderate	5.6%	8.8%	22.5%			
Too hard BM	Lack	77.8%	52.9%	52.5%	-0.323	0.002	0.015
	Mild	11.1%	29.4%	20.0%			
	At least moderate	11.1%	17.6%	27.5%			

Abbreviations: BM: bowel movement; eGFR: estimated glomerular filtration rate

Since constipation is a common side effect of certain drugs, we estimated prevalence ratio (PR) of constipation in patients according to their drug-use patterns, adjusted to demographics, eGFR tercile and comorbidities (see details in Methods). The frequency of drug-taking is summarized in Supplementary material, *Table S2*. As shown in Table 3, for constipation diagnosed with the BSFS, besides female sex and increasing age, taking diuretics was independently associated with increased PR of constipation (adjusted PR 2.86, 95% CI 1.28-6.37, P = 0.01). In contrast, paracetamol and low eGFR (≤ 32 ml/min/1.73 m^2) were associated with increased PR of FC, whereas taking NSAIDs was independently associated with lower PR of FC (Supplementary material, *Table S3*). No drug was independently associated with having less than once BM a day (Supplementary material, *Table S4*).

Health-related quality of life

SF-36v2 is a tool commonly used to assess the HRQoL that has been validated also in Poland [23]. To evaluate associations between HRQoL and GI symptoms, we performed linear regressions that were adjusted for demographic and clinical data (columns 'Adjusted univariate analyses' in Table 4 and Supplementary material, *Tables S5-S10*). We found that the presence of discomfort in the abdomen was independently associated with worse scores in all HRQoL domains (Table 4 and Supplementary material, *Tables S5-S10*). Similarly, the presence of pain in the abdomen was associated with worse assessment of all, save RE, HRQoL domains (Table 4

and Supplementary material, *Tables S5-S9*). Also, painful BMs reporting was significantly associated with lower scores in MH, VT, SF, and RE (Table 4 and Supplementary material, *Tables S8-S10*). Defecation less frequently than mean once a day was associated with lower scores in PF, RP and MH (Table 4 and Supplementary material, *Tables S5-S6*). FC was associated with BP and VT (Supplementary material, *Tables S7-S8*). Interestingly, BSFS-diagnosed constipation was not associated with a lower score in any HRQoL domain.

Table 3. Poisson regression models showing variables significantly and independently associated with prevalence ratio of constipation diagnosed with the Bristol Stool Form Scale

Variable	Univariate analyses (each row represents separate model)		Multiple regression	
	PR (95% CI)	*P* value	PR (95% CI)	*P* value
Use of diuretics	2.72 (1.21-6.14)	0.016	2.86 (1.28-6.37)	0.010
Age, years	1.015 (0.99-1.04)	0.231	1.053 (1.01-1.10)	0.012
Female sex	1.57 (0.83-2.97)	0.161	120.72 (2.54-5728.74)[a]	0.015
Female sex × age interaction	-	-	0.935 (0.89-0.99)	0.015
BMI, kg/m²	1.004 (0.94-1.07)	0.897	1.02 (0.96-1.09)	0.528
eGFR tercile:				
High	reference	-	reference	-
Medium	1.43 (0.54-3.75)	0.469	1.38 (0.58-3.33)	0.468
Low	1.30 (0.50-3.42)	0.592	1.74 (0.68-4.49)	0.250
Diabetes	1.05 (0.53-2.06)	0.891	0.81 (0.41-1.61)	0.546
Heart failure	1.09 (0.51-2.33)	0.832	0.84 (0.38-1.87)	0.667
Hypothyroidism	1.23 (0.55-2.73)	0.616	1.10 (0.50-2.37)	0.817
Depression	1.46 (0.47-4.48)	0.512	1.10 (0.31-3.89)	0.879

Abbreviations: BMI: body mass index; CI: confidence interval; eGFR: estimated glomerular filtration rate; PR: prevalence ratio

[a] Due to significant interaction with age, being women at median age of 69 was associated with PR approx. 1.17 compared to men in this age (exp(ln(120.72) + ln(1.053)×69 + ln(0.935)×69) / exp(ln(1.053)×69)).

Table 4. Mental health (MH) score regressions adjusted to sex, age, BMI, eGFR tercile, and comorbidities for constipation and constipation-related symptoms

Variable	Adjusted univariate analyses (row represents separate model)			Selected adjusted multiple regression (AIC 865.9, R^2 = 0.352, *P* < 0.001)	
	Coefficient	*P* value	AIC	Coefficient (95% CI)	*P* value
Frequency of defecation:			886.2		
Once a day	reference	-		reference	-
Less than once a day	-15.35	<0.001		-10.63 (-18.96, -2.31)	0.013
More than once a day	-3.21	0.507		-0.08 (-9.25, 9.08)	0.986
Discomfort in abdomen [a]	-17.31	<0.001	911.1	-14.07 (-21.69, -6.45)	<0.001
Discomfort in abdomen:			912.5	-	-
Lack	reference	-			
Mild	-15.41	<0.001			
Medium/severe	-19.50	<0.001			
Pain in abdomen [a]	-16.18	<0.001	917.1	-	-
Pain in abdomen:			919.1	-	-
Lack	Reference	-			
Mild	-16.03	<0.001			
Medium/severe	-16.51	0.009			
Bloating in abdomen [a]	-10.68	0.005	925.0	-	-
Bloating in abdomen:			924.1	-	-
Lack	reference	-			
Mild	-7.35	0.087			
Medium/severe	-15.90	0.002			
Painful BM [a]	-13.97	0.013	926.8	-	-
BM that was too small [a]	-11.36	0.013	926.8	-	-
BM that was too small:			926.9	-	-
Lack	reference	-			
Mild	-7.03	0.214			
Medium/severe	-16.86	0.008			
Stomach cramps [a]	-10.98	0.014	926.9	-	-
Straining/squeezing [a]	-9.94	0.011	926.39	-	-
Straining/squeezing:			926.35		
Lack	Reference	-			
Mild	-6.60	0.149			
Medium/severe	-14.22	0.005			
Feeling false alarm [a]	-11.91	0.015	927.1		

Abbreviations: AIC: Akaike information criterion; BM: bowel movement.

[a] presence of the symptom, regardless of its severity

To find out how many and which of the symptoms should be considered assessing the HRQoL, we have selected the balanced adjusted multiple regression model for each HRQoL domain (columns 'Selected adjusted multiple regression' in Table 4 and Supplementary material, *Tables S5-S10*). The following symptoms were in at least two models: pain in the abdomen (PF, RP, BP, SF), discomfort in the abdomen (VT, SF), altered frequency of defecation (PF, RP), having BMs that were too hard (BP, VT), too small (PF, RE) or painful (VT, RE). Such selected models explained 33.7-53.0% of the variability of the HRQoL scores (R^2 reported in columns 'Selected adjusted multiple regression' in Table 4 and Supplementary material, *Tables S5-S10*), whereas models based only on sex, age, BMI, eGFR tercile and comorbidities explained only 13.6-34.6% of the variability.

Discussion

Our study aimed to determine the prevalence of constipation-related symptoms in conservatively-treated CKD patients, as well as to verify the relationship between them and HRQoL. Using validated questionnaires, we found that a number of gastrointestinal symptoms are frequently reported by CKD patients, and that presence of symptoms was associated with worse HRQoL.

Since constipation prevalence varies widely due to differences in the used constipation definition [2, 28–30], we used three ways to define constipation: the BSFS, Rome III criteria, and the decreased frequency of BM per week. In the general population of Europe, the mean value of the reported constipation rates is 17.1% [2]; that is a lower value than the prevalence of FC and BSFS-based constipation in our study; that is 18.9% and 28.9%, respectively. Recently published comprehensive review article about constipation in CKD revealed that despite strong evidence on higher prevalence of constipation in dialysis patients (23.8-71.7% and 14.2-28.9% of HD and PD patients, respectively [16]), information is scarce on the epidemiology of constipation among patients with conservatively-treated patients [18]. To our knowledge, up-to-date only two studies that included conservatively-treated CKD patients used Rome III criteria and BSFS to determine the prevalence of constipation [12, 30]. In the first, FC and BSFS-diagnosed constipation were recognized in 5% and 19% of 21 non-dialysis ESRD patients, respectively. In the second, FC and BSFS-diagnosed constipation were recognized in 35% and 33% of 43 non-dialysis nondiabetic patients with eGFR <45 mL/min/1.73 m^2, respectively. Since the number of included participants was limited, we agree with authors of the above-mentioned review article that there is a need for more data on constipation epidemiology among conservatively-treated CKD patients [18]. We not only did determine the prevalence in more than twofold bigger population of patients, but also found factors associated with the altered prevalence of constipations.

Indeed, we found out that paracetamol and diuretics were independently associated with increased PR of constipation diagnosed with Rome III criteria and BSFS, respectively. Even though all these drugs have been associated with constipation in other patients populations [31–33], the mechanisms leading to such side-effects are not clear. Regarding paracetamol, Chang et al. suggested that its pro-constipation properties can be attributed to the anti-serotonergic effects of paracetamol; however, it was not investigated directly yet [32]. It is hypothesized that diuretics can cause constipation secondary to dehydration, electrolyte disturbances, or, less probably, directly suppressing gut motility [33, 34]. In the presented study, we confirmed associations between the presence of constipation and lower HRQoL. We have demonstrated that FC is independently associated with BP and VT, parts of SF-36v2 physical and mental summary components, respectively. Similarly, Zhang et al. have shown that FC is associated with lower scores in both physical and mental summary components of HRQoL in both HD and PD patients [17]. Interestingly, our study has indicated that constipation diagnosed with BSFS is not associated with worse HRQoL in conservatively-treated CKD patients. It is highly interesting as previous studies did not perform such analyses. As the BSFS is a clinical surrogate of whole-gut and colonic transit [35], we hypothesize that the deterioration in HRQoL of constipated CKD patients is not a consequence of delayed gut transit. More probable, given the associations between functional constipation and decreased HRQoL, and following the knowledge about the pathophysiology of functional gastrointestinal disorders, decreased HRQoL might be a manifestation of a disturbance in bidirectional relationship of the gastrointestinal tract and nervous system [36].

Even though we have not seen an association between constipation diagnosed with BSFS and worse HRQoL, assessment of BSFS should not be neglected in CKD patients. Ramos et al. found that so defined constipation was associated with significantly higher serum concentration of *p*-cresyl sulfate, a microbial-derived uremic toxin [12]. Interestingly, the same study failed to show an association between FC and the serum concentration of either *p*-cresyl sulfate or indoxyl sulfate. Since cardiovascular disease is the

leading cause of death in CKD and there are data suggesting that constipation is associated with increased cardiovascular risk [5, 37], further studies are needed to compare clinical associations and cardiovascular mortality between CKD patients with constipation according to BSFS versus Rome criteria.

Using the PAC-SYM questionnaire, we have shown that the severity of straining to pass BM, as well as painful, incomplete, or too hard BM correlated with the deterioration of kidney function. That is, patients with low eGFR assessed the severity of these symptoms as at least moderate from 1.8 (straining to pass BM) to even 4 (incomplete BM) times more frequently than patients with high eGFR. Moreover, low eGFR was independently associated with a 2.85 times higher prevalence of FC in comparison to high eGFR. The high and low eGFR terciles in our study share high similarity to G1-G3a and G4-G5 CKD stages, respectively. Unfortunately, patients with G3b CKD were also present as a small fractions of upper tercile (8% of individuals in this tercile) and lower tercile (35% of individuals in this tercile), thus direct translation of the results into CKD stages is impossible due to high disproportion in the number of recruited patients across stages of CKD.

Knowing the prevalence of constipation and related symptoms and their deteriorating impact on HRQoL, it is important to find effective methods of lower gastrointestinal symptoms management for CKD patients. Firstly, nonpharmacological treatment should be considered, i.e. increase in physical activity and improvement of diet [38]. Indeed, one can recommend a fiber-rich diet because it shortens intestinal transit time (via bulking effect [39]) and, additionally, is a part of healthy dietary patterns that are associated with lower mortality in CKD patients [40]. However, based on the high prevalence of bloating among CKD patients in our study, as well as that some CKD patients require fluid intake restriction, the recommendation of a diet rich in fiber should be given cautiously. In fact, the high-fiber diet can lead to exacerbation of flatulence (via retardation of intestinal gas propulsion [41])[42], and water restriction reduces the pro-motile effect of fiber [43]. Unfortunately, there are no clinical trials assessing the efficacy of diet modification on constipation reduction in conservatively-treated CKD patients. Interestingly, the consumption of 40 g of raw almonds daily for four weeks was safe and improved both BSFS-diagnosed constipation and HRQoL in HD patients [44]. In view of our findings, similar trials are desirable in the population of conservatively-treated CKD patients.

The next step of constipation management is the introduction of pharmacotherapy [18]. Since there is no data on the safety and efficacy of laxatives in CKD patients, one should take into account that some of them can have limited efficacy in patients restricting fluid intake (stool softeners, i.e. docusate sodium/calcium) and some may exacerbate constipation-related symptoms, e.g. flatulence (lactulose). As the majority of CKD patients in our study reported bloating, anti-foaming agents—simethicone and dimethicone—should be taken into account because they are effective in relieving abdominal distension and flatulence in functional gastrointestinal disorders [45, 46]. Moreover, alleviation of abdominal bloating in constipated patients is achievable using new laxative drugs: lubiprostone (a type-2 chloride channel activator), linaclotide (a guanylate cyclase-C receptor agonist), prucalopride (selective 5-HT4 receptor agonist), and elobixibat (an ileal bile acid transporter inhibitor) [47–50].

Interestingly, according to animal studies, a part of drugs used in constipation treatment can possess nephroprotective properties. In adenine-induced CKD rat model, lactulose—a prebiotic disaccharide—was shown to possess nephroprotective properties (i.e. suppressed tubulointerstitial fibrosis) via reduction of microbiota-derived uremic toxin, indoxyl sulfate [51]. Since lactulose reduces microbiota-derived uremic toxins, indoxyl sulfate and *p*-cresol, in humans [52], it can be hypothesized that introduction of such constipation treatment can additionally slow the progression of CKD. Similarly, lubiprostone and linaclotide can possess nephroprotective properties via improving the gut microbiota and intestinal environment as was demonstrated in adenine-induced CKD mouse model [53, 54]. However, the nephroprotective properties of these laxatives should be confirmed in clinical trials with conservatively-treated CKD patients. Such studies could also determine whether the treatment of constipation significantly improves HRQoL in this population. In a multicenter, observational study of hemodialysis patients with FC, elobixibat significantly increased the frequency of BM and improved patients' HRQoL [55]. Furthermore, based on mechanistic insights into the "gut–kidney–heart" axis, Sumida and Kovesdy have recently hypothesized that the administration of laxatives might be a gut microbiota-targeted therapeutic intervention for reduction cardiovascular risk in patients with CKD [37].

The relatively small number of surveyed patients, lack of healthy control group, lack of information about proteinuria, direct usage of Rome III criteria in authors' questions instead of validated diagnostic questionnaire to diagnose FC, and a

cross-sectional character of the study can limit the importance of obtained results. However, our study possesses also considerable advantages such as comprehensiveness (detailing the prevalence of constipation and constipation-related symptoms, finding factors associated with the altered prevalence of constipation, and analysis of associations between the symptoms and HRQoL domains), inclusion of more than twofold bigger population than in previous similar studies, and use of the method of *P* values correction limiting the probability of false discovery (a type I error). Our study, as one of the first in the field, should prompt researchers to determine the epidemiology of constipation and related symptoms in conservatively-treated CKD patients, as well as to establish the biochemical, clinical and patient-oriented benefits of their treatment.

Supplementary Material

Supplementary tables.
http://www.medsci.org/v17p2954s1.pdf

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Competing Interests

The authors have declared that no competing interest exists.

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Appendix

Tables S5-S10: Univariate analyses of constipation and constipation-related symptoms are adjusted to sex, age, BMI, eGFR tercile, and comorbidities. Selection of multiple regression model is described in the Methods section in the manuscript. [a] represents presence of the symptom, regardless of its severity.

Table S1. Internal consistency reliability and construct validity of SF-36v2 subscales

	Internal consistency reliability		Construct validity	
SF-36v2 subscale	Cronbach's alpha	Average inter-item correlation	Convergent validity [a]	Discriminant validity [b]
PF	0.934	0.587	0.65-0.80	0.32-0.68
RP	0.944	0.810	0.82-0.92	0.42-0.77
BP	0.916	0.846	0.87	0.41-0.66
GH	0.646	0.267	0.34-0.51	0.23-0.54
VT	0.834	0.557	0.61-0.71	0.40-0.65
SF	0.818	0.691	0.69	0.49-0.61
RE	0.962	0.893	0.92-0.93	0.42-0.72
MH	0.846	0.523	0.62-0.72	0.26-0.71

[a] Item-own scale correlation; poor convergent validity is indicated when items do not correlate .40 or higher with their hypothesized scale score. [b] Item-other scale correlation; poor discriminant validity is indicated when items correlate significantly higher with competing scales than with their hypothesized scale.

We found that nearly all subscales were reliable (Cronbach's alpha above 0.80), but General Health (GH) subscale was not. Average inter-item correlations exceeding 0.5 for the all rest of subscales proved reliability and suggested redundant character of some questions in the subscales. Moreover, convergent validity of the Polish version of SF-36v2 subscales, besides GH, was confirmed as all the correlation coefficients of items within these subscales exceeded the 0.40 criterion. Similarly, 4 out of 5 items in GH subscale and 1 item out of 5 items in MH subscale (MH05: happiness) failed their discriminant validity as their correlation coefficients with other scales were higher than correlation coefficients with their own subscales.

Abbreviations: BP, bodily pain; GH, general health perceptions; MH, general mental health; PF, physical functioning; RE, role limitations due to emotional problems; RP, role limitations due to physical health problems; SF, social functioning; VT, vitality.

Table S2. Pharmacological treatment of the study population.

	All	**Patients defecating less than once a day**	**Patients meeting criteria of functional constipation**	**Patients meeting Bristol scale criteria of constipation**
N No data, n	111	38 5	21 0	28 14
Beta blockers, n (%)	75 (67.6)	25 (65.8)	14 (66.7)	19 (67.9)
Calcium channel blockers, n (%)	58 (52.3)	26 (68.4)	11 (52.4)	16 (57.1)
Diuretics, n (%)	60 (54.1)	23 (60.5)	9 (42.9)	21 (75.0)
NSAIDs, n (%)	24 (21.6)	7 (18.4)	2 (9.5)	4 (14.3)
Paracetamol, n (%)	14 (12.6)	8 (21.1)	5 (23.8)	4 (14.3)
Calcium supplements, n (%)	21 (18.9)	6 (15.8)	3 (14.3)	6 (21.4)
Vitamin D, n (%)	34 (30.6)	15 (39.5)	11 (52.4)	8 (28.6)
Iron, n (%)	8 (7.2)	2 (5.3)	1 (4.8)	3 (10.7)
Hypnotics, n (%)	7 (6.3)	1 (2.6)	2 (9.5)	1 (3.6)

Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs.

Table S3. Poisson regression model showing variables significantly and independently associated with altered prevalence ratio of presence of at least 2 criteria of functional constipation.

Variable	Univariate analyses (row represents separate model)		Multiple regression	
	PR (95% CI)	*P* value	PR (95% CI)	*P* value
Use of vitamin D	2.30 (1.06, 5.00)	**0.035**	1.59 (0.76, 3.31)	0.214
Use of paracetamol	2.26 (0.97, 5.25)	0.058	2.67 (1.07, 6.64)	**0.035**
Use of NSAIDs	0.39 (0.10, 1.58)	0.188	0.34 (0.11, 1.00)	**0.049**
Age	1.02 (0.99, 1.04)	0.273	1.03 (0.99, 1.06)	0.152
Female sex	1.61 (0.72, 3.57)	0.239	2.10 (0.85, 5.23)	0.109
BMI	0.97 (0.91, 1.04)	0.369	1.02 (0.95, 1.08)	0.617
eGFR tercile:				
- High	reference	-	reference	-
- Medium	1.40 (0.41, 4.78)	0.590	0.79 (0.24, 2.61)	0.699
- Low	2.61 (0.91, 7.47)	0.074	2.85 (1.12, 7.28)	**0.028**
Diabetes	0.55 (0.20, 1.52)	0.252	0.37 (0.11, 1.23)	0.105
Heart failure	0.70 (0.22, 2.17)	0.534	0.67 (0.23, 2.00)	0.477
Hypothyroidism	1.35 (0.51, 3.55)	0.540	1.33 (0.55, 3.21)	0.522
Depression	2.31 (0.73, 7.32)	0.154	1.95 (0.74, 5.14)	0.177

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; NSAIDs, nonsteroidal anti-inflammatory drugs.

Table S4. Poisson regression model showing variables significantly and independently associated with altered prevalence ratio of having less than 7 bowel movements per week.

Variable	Univariate analyses (row represents separate model)		Multiple regression	
	PR (95% CI)	*P* value	PR (95% CI)	*P* value
Use of vitamin D	1.50 (0.89, 2.53)	0.129	1.38 (0.72, 2.65)	0.337
Use of paracetamol	1.84 (1.06, 3.18)	**0.030**	1.53 (0.72, 3.27)	0.271
Use of calcium channel blocker	2.00 (1.12, 3.56)	**0.018**	1.72 (0.98, 3.00)	0.059
Age	0.99 (0.98, 1.01)	0.417	0.99 (0.97, 1.01)	0.288
Female sex	1.70 (1.00, 2.90)	**0.049**	1.86 (0.96, 3.61)	0.066
BMI	0.98 (0.93, 1.04)	0.527	1.01 (0.95, 1.07)	0.845
eGFR tercile:				
- High	Reference	-	Reference	-
- Medium	1.50 (0.73, 3.09)	0.271	1.42 (0.70, 2.87)	0.334
- Low	1.67 (0.84, 3.31)	0.144	1.79 (0.87, 3.67)	0.114
Diabetes	0.87 (0.48, 1.57)	0.636	0.79 (0.40, 1.54)	0.484
Heart failure	0.75 (0.36, 1.56)	0.436	0.80 (0.37, 1.70)	0.559
Hypothyroidism	1.02 (0.51, 2.07)	0.949	0.80 (0.36, 1.76)	0.578
Depression	1.16 (0.38, 3.53)	0.787	0.68 (0.21, 2.20)	0.521

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate.

Table S5. Adjusted physical functioning (PF) score regressions and selected multiple regression.

Variable	Adjusted univariate analyses (row represents separate model)			Selected multiple regression (AIC 903.0, $R^2 = 0.530$, $P < 0.001$)	
	Coefficient	*P* value	AIC	Coefficient (95% CI)	*P* value
Frequency of defecation: :			926.5		
- Once a day	reference	-		reference	-
- Less than once a day	-19.30	**<0.001**		-8.72 (-19.56, 2.12)	0.113
- More than once a day	-0.887	0.880		3.83 (-7.12, 14.79)	0.489
Discomfort in abdomen [a]	-13.70	**0.006**	970.6	-	-
Discomfort in abdomen:			972.3		
- Lack	reference	-		-	-
- Mild	-11.97	**0.048**			
- Medium/severe	-15.88	**0.017**			
Pain in abdomen [a]	-24.48	**0.001**	953.0	-19.28 (-29.51, -9.04)	**<0.001**
Pain in abdomen:			954.1		
- Lack	reference	-		-	-
- Mild	-26.76	**<0.001**			
- Medium/severe	-19.64	**0.009**			
BM that was too small [a]	-18.89	**0.001**	966.4	-11.08 (-21.88, -0.28)	**0.044**
BM that was too small:			964.7		
- Lack	reference	-		-	-
- Mild	-11.00	0.116			
- Medium/severe	-28.08	**<0.001**			
Stomach cramps [a]	-16.58	**0.002**	968.6	-	-
Stomach cramps:			970.1		
- Lack	reference	-		-	-
- Mild	-18.75	**0.003**			
- Medium/severe	-11.50	0.216			

Table S6. Adjusted role limitations due to physical health problems (RP) score regressions and selected multiple regression.

Variable	Adjusted univariate analyses (row represents separate model)			Selected multiple regression (AIC = 945.0, R^2 = 0.398, P < 0.001)	
	Coefficient	*P* value	AIC	Coefficient (95% CI)	*P* value
Frequency of defecation: :			963.0		
- Once a day	reference	-		Reference	-
- Less than once a day	-20.52	**<0.001**		-11.64 (-23.82, 0.54)	0.061
- More than once a day	-4.84	0.470		-1.71 (-14.53, 11.11)	0.792
Functional constipation	-19.35	**0.006**	1014.5	-	-
Discomfort in abdomen [a]	-15.63	**0.005**	1004.7	-	-
Discomfort in abdomen:			1005.5		
- Lack	reference	-		-	-
- Mild	-11.59	0.087			
- Medium/severe	-20.29	**0.005**			
Pain in abdomen [a]	-22.91	**<0.001**	996.4	-16.72 (-28.80, -4.64)	**0.007**
Pain in abdomen:			998.4		
- Lack	reference	-		-	-
- Mild	-22.46	**<0.001**			
- Medium/severe	-23.87	**0.007**			
BM that was too hard [a]	-14.41	**0.009**	1005.8	-	-
BM that was too hard			1005.0		
- Lack	reference	-		-	-
- Mild	-8.46	0.197			
- Medium/severe	-21.73	**0.003**			
BM that was too small:			1006.76		
- Lack	reference	-		-	-
- Mild	-5.17	0.510			
- Medium/severe	-24.58	**0.005**			

Stomach cramps [a]	-19.23	**0.002**	1002.6	-	-
Stomach cramps: - Lack - Mild - Medium/severe	 reference -21.17 -14.71	 - **0.003** 0.159	1004.3	-	-
Straining/squeezing [a]	-16.76	**0.002**	1002.6	-9.358 (-19.86, 1.14)	0.080
Straining/squeezing: - Lack - Mild - Medium/severe	 Reference -17.54 -15.76	 - **0.006** **0.024**	1004.6	-	-

Table S7. Adjusted bodily pain (BP) score regressions and selected multiple regression.

Variable	Adjusted univariate analyses (row represents separate model)			Selected multiple regression model (AIC 987.6, $R^2 = 0.366$, $P < 0.001$)	
	Coefficient	*P* value	AIC	Coefficient (95% CI)	*P* value
Functional constipation	-16.17	**0.020**	1010.6	-	-
Bloating in abdomen [a]	-13.01	**0.012**	1000.2	-	-
Bloating in abdomen:			998.3		
- Lack	reference	-		-	-
- Mild	-7.71	0.185			
- Medium/severe	-21.31	**0.002**			
Pain in abdomen [a]	-19.75	**<0.001**	994.0	-16.03 (-27.11, -4.95)	**0.005**
Pain in abdomen:			995.8		
- Lack	reference	-		-	-
- Mild	-18.50	**0.005**			
- Medium/severe	-22.42	**0.010**			
BM that was too hard [a]	-14.07	**0.008**	999.4	-13.11 (-23.08, -3.14)	**0.010**
BM that was too hard			999.2		
- Lack	reference	-		-	-
- Mild	-8.95	0.160			
- Medium/severe	-20.37	**0.004**			
Discomfort in abdomen [a]	-14.31	**0.008**	999.4	-	-
Discomfort in abdomen:			998.6		
- Lack	reference	-		-	-
- Mild	-8.26	0.205			
- Medium/severe	-21.28	**0.002**			
Feeling false alarm:			1000.3		
- Lack	Reference	-		Reference	-
- Mild	-6.47	0.408		1.56 (-13.50, 16.62)	0.838
- Medium/severe	-29.45	**0.006**		-20.85 (-41.07, -0.64)	**0.043**

Table S8. Adjusted vitality (VT) score regressions and selected multiple regression.

Variable	Adjusted univariate analyses (each row represents separate model)			Selected adjusted regression (AIC 909.1, $R^2 = 0.373$, $P < 0.001$)	
	Coefficient	*P* value	AIC	Coefficient (95% CI)	*P* value
Discomfort in abdomen [a]	-13.62	**<0.001**	920.6	-10.78 (-18.24, -3.32)	**0.005**
Discomfort in abdomen:			920.1		
- Lack	reference	-		-	-
- Mild	-9.63	**0.042**			
- Medium/severe	-18.21	**<0.001**			
BM that was too hard			921.8		
- Lack	reference	-		reference	-
- Mild	4.69	0.314		7.34 (-1.36, 16.04)	0.097
- Medium/severe	-15.61	**0.002**		-12.66 (-22.06, -3.27)	**0.009**
Painful BM [a]	-12.98	**0.022**	928.0	-10.26 (-20.59, 0.06)	0.051
Bloating in abdomen [a]	-9.33	**0.015**	927.3	-	-
Bloating in abdomen:			927.0		
- Lack	reference	-		-	-
- Mild	-6.29	0.148			
- Medium/severe	-14.11	**0.006**			
Pain in abdomen [a]	-15.15	**<0.001**	919.5	-	-
Pain in abdomen:			921.5		
- Lack	reference	-		-	-
- Mild	-14.66	**0.002**			
- Medium/severe	-16.19	**0.012**			
Functional constipation	-10.25	**0.048**	938.6	-	-
Stomach cramps [a]	-11.98	**0.007**	925.7	-	-
Stomach cramps:			927.7		
- Lack	reference	-		-	-
- Mild	-11.56	**0.026**			
- Medium/severe	-12.95	0.090			

Feeling false alarm [a]	-12.49	**0.010**	926.6	-	-
Feeling false alarm: - Lack - Mild - Medium/severe	 reference -8.46 -20.18	 - 0.145 **0.011**	926.8	-	-

Table S9. Adjusted social functioning (SF) score regressions and selected multiple regression

Variable	Adjusted univariate analyses (row represents separate model)			Selected adjusted multiple regression (AIC 982.0, $R^2 = 0.337$, $P < 0.001$)	
	Coefficient	*P* value	AIC	Coefficient (95% CI)	*P* value
Discomfort in abdomen [a]	-16.61	**0.001**	986.6	-	-
Discomfort in abdomen: - Lack - Mild - Medium/severe	 reference -12.36 -21.50	 - **0.046** **0.001**	987.0	 Reference -5.16 (-18.31, 8.00) -21.32 (-37.84, -4.80)	 - 0.438 **0.012**
Pain in abdomen [a]	-18.84	**0.001**	985.1	-	-
Pain in abdomen: - Lack - Mild - Medium/severe	 reference -22.51 -11.04	 - **0.000** 0.178	985.3	 Reference -16.44 (-29.95, -2.92) 6.08 (-14.57, 26.73)	 - **0.018** 0.560
Painful BM [a]	-17.61	**0.016**	991.8	-	-
Straining/squeezing [a]	-12.21	**0.016**	991.7	-	-

Table S10. Adjusted role limitations due to emotional problems (RE) score regressions and selected multiple regression.

Variable	Adjusted univariate analyses (row represents separate model)			Selected adjusted regression (AIC 983.5, $R^2 = 0.359$, $P < 0.001$)	
	Coefficient	*P* value	AIC	Coefficient (95% CI)	*P* value
Discomfort in abdomen [a]	-16.99	**0.001**	987.0	-12.29 (-22.67, -1.90)	**0.021**
Discomfort in abdomen:			988.5		
- Lack	reference	-		-	-
- Mild	-14.60	**0.020**			
- Medium/severe	-19.74	**0.003**			
Painful BM [a]	-19.49	**0.008**	991.2	-13.22 (-27.37, 0.94)	0.067
BM that was too small [a]	-15.41	**0.009**	991.5	-9.11 (-20.75, 2.52)	0.123
Straining/squeezing [a]	-14.12	**0.005**	990.3	-	-
Straining/squeezing:			992.3		
- Lack	Reference	-		-	-
- Mild	-14.47	**0.016**			
- Medium/severe	-13.67	**0.037**			

ORIGINAL ARTICLE

Associations between symptoms of constipation and sleep quality in patients with nondialysis chronic kidney disease: a cross-sectional study

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ABSTRACT

INTRODUCTION Sleep disturbances, similarly to constipation-related symptoms, are common problems in patients with chronic kidney disease (CKD) and are associated with worse health-related quality of life.

OBJECTIVES The aim of the study was to investigate sleep problems in conservatively treated patients with CKD and to assess association between sleep quality and constipation in that population.

PATIENTS AND METHODS In this cross-sectional study, 100 conservatively treated outpatients with CKD filled questionnaires addressing sleep quality (The Medical Outcomes Study 12-item Sleep Scale–Revised [MOS-Sleep-R]) and constipation-related symptoms (PAC-SYM, Rome III criteria).

RESULTS The T scores of none of the assessed sleep domains differed across the estimated glomerular filtration rate terciles (all $P > 0.05$). The scores from the PAC-SYM abdominal and stool subscales correlated with all assessed sleep quality domains. In both univariable and multivariable regression models adjusted for key clinical data, functional constipation, less than 7 bowel movements a week, abdominal discomfort, and pain as well as too small bowel movements were independently associated with increased prevalence ratio of decreased sleep quality.

CONCLUSIONS In patients with nondialysis CKD, sleep disorders might have common etiological factors with constipation-related symptoms.

INTRODUCTION Sleep is a complex physiological process that is crucial for maintaining well-being and overall health. Even though sleep disorders are prevalent, the underlying precise pathophysiological mechanisms are not always well understood.[1]

Chronic kidney disease (CKD) is a common condition (9.1%–13.4% of the global population)[2,3] that is defined as abnormalities of kidney structure or function, present for more than 3 months, with implications for health.[4] That is, a decline in kidney function adversely affects multiple organs which leads to a decrease in both physical and mental health-related quality of life (HRQOL).[5]

As evidenced by recent meta-analyses, there is a high prevalence of several sleep disorders in patients with CKD.[6-8] Among patients with nondialysis CKD, pooled prevalence estimates (and 95% CIs) of sleep apnea, insomnia, excessive daytime sleepiness, and restless leg syndrome were 38% (21%–70%), 33.3% (22.2%–46.1%), 22% (18%–28%), and 9.9% (5.4%–17.5%), respectively.[6-8] The prevalence of sleep disorders is even higher among dialysis patients, and is partially normalized after kidney transplantation.[6,7,9] Since many studies failed to show an association between sleep quality and CKD progression, a greater focus has been placed on finding other factors associated with the increased prevalence of sleep disorders in patients with CKD.[10-14] Uncovering the manageable causes of sleep disorders in this population would be of great benefit.

Interestingly, there are factors associated both with CKD and sleep disorders, such as decreased melatonin level, increased body mass index, and functional constipation.[15-18] However,

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WHAT'S NEW?

Sleep disorders are prevalent in patients with chronic kidney disease; however, the underlying precise pathophysiological mechanisms are poorly understood. In our study, we found that constipation and certain gastrointestinal symptoms commonly coexist with decreased sleep quality. Uncovering the manageable causes of sleep disorders in patients with chronic kidney disease would be of great benefit, and our study sheds light on new perspectives on these causes that should be verified in clinical trials.

the association between constipation-related symptoms and quality of sleep in patients with CKD has not been reported yet.

The aim of the study was to describe sleep problems in conservatively treated patients with CKD, and to explore the association between sleep problems and constipation-related symptoms in that population.

PATIENTS AND METHODS This study was conducted as part of a broad project that aimed to comprehensively assess the relationship between lower gastrointestinal symptoms and quality of life in conservatively treated CKD patients. The full methodology of the study was described previously.[19] The study protocol was approved by the Bioethical Committee for Scientific Research at the Medical University of Gdańsk, Poland (NKBBN/426–56/2018).

Study population Briefly, we screened 150 and recruited 111 outpatients visiting the Nephrological Outpatient Clinic (University Clinical Centre in Gdańsk) between June 2018 and December 2019. Participants were eligible for the study if they were adults (>18 years old) diagnosed with CKD. Exclusion criteria were as follows: current dialysis or a history of dialysis; a history of kidney transplantation; cognitive or visual deficits that rendered a patient unable to answer the questionnaire; serious illness in an acute treatment phase. All patients were informed about the nature and purpose of the study. As the research was based on voluntarily filled anonymous surveys, additional written informed consent was not required.

Measures Participants were asked to voluntarily complete a battery of questionnaires. Besides questionnaires reported in the previous study assessing HRQOL (the Polish 36-item Short Form Health Survey version 2.0, known as SF-36v2) and symptoms of constipation (the Patient Assessment of Constipation-Symptoms [PAC-SYM] questionnaire; simple questions containing Rome III criteria of functional constipation, question about the number of bowel movements [BMs] per week, and the Bristol Stool Form Scale [BSFS]), patients were asked to fill the Medical Outcomes Study Sleep Scale–Revised (MOS-Sleep-R). BSFS constipation was defined as type 1 ("separate hard lumps, like nuts [difficult to pass]") or type 2 ("sausage-shaped but lumpy") stool form.

The MOS-Sleep-R questionnaire includes 12 items that measure 6 dimensions of sleep with a 4-week recall period: sleep disturbance (4 items), daytime somnolence (3 items), sleep adequacy (2 items), snoring (1 item), awakening due to shortness of breath / headache (1 item), and sleep quantity (1 item). The sleep disturbance subscale addresses problems both with sleep initiation and maintenance. The somnolence subscale measures daytime sleepiness. Sleep adequacy represents morning restedness and getting the needed amount of sleep. Ten items are measured on a 5-point Likert scale ranging from "all of the time" to "none of the time." Two additional items address time to fall asleep (from "0–15 minutes" to "more than 60 minutes") and an average number of hours slept each night (7–8 hours are interpreted as "optimal" sleep quantity). Higher scores indicate better sleep outcomes. Scoring points are transformed into standardized T scores (mean [SD], 50 [10]) based on data from a 2009 United States internet-based general population survey.[20] The summary measure of sleep quality (called the Sleep Problems Index II) is derived from 9-item scores; due to the method of scoring, it is reported as "Sleep Quality" in this paper (the higher the score, the better quality of sleep).

The SF-36v2 questionnaire consists of 36 items that assess 8 dimensions of HRQOL: physical functioning; role limitations due to problems with physical health; bodily pain; vitality; social functioning; role limitations due to emotional problems; mental health; and general health perception. Higher scores indicate better HRQOL. Since the general health scale in the Polish version of the SF-36v2 is neither reliable nor valid,[19] we did not use the results of this domain in this study. To use both the MOS-Sleep-R and the SF-36v2, a noncommercial license agreement was made between JR and OptumInsight Life Sciences, Inc (license no., QM044526; Johnston, United States). Both questionnaires were scored using the desktop scoring software PRO CoRE Version 1.4 provided by Optum.

Data on gender, age, body weight, height, body mass index, estimated glomerular filtration rate (eGFR) based on CKD-EPI formula, etiology of CKD, comorbidities, and taken medications were collected by a physician, as reported previously.[19]

Statistical analysis Normal distribution of data was tested using the Shapiro–Wilk test. Continuous variables with nonnormal distribution were presented as medians and interquartile ranges (IQRs) and differences in their values between groups were presented as the Hodges–Lehmann estimate. Categorical variables were presented as a percentage share of the obtained data. Patient groups were compared using the Mann–Whitney test, the Kruskal–Wallis test (with a pairwise post hoc Dunn tests), and Pearson χ^2 test. Statistical

testing was done with JASP 0.13.1 and Python libraries: Pandas,[21] Pingouin,[22] Statsmodels.[23] *P* values of less than 0.05 were considered significant. To adjust for multiple comparisons, all *P* values of post hoc tests were corrected using the Bonferroni–Holm adjustment method.

Due to a high disproportion in the number of patients across stages of CKD, patients were divided into 3 groups according to eGFR terciles: with low eGFR (≤32 ml/min/1.73 m^2), medium eGFR (33–43 ml/min/1.73 m^2), and high eGFR (≥44 ml/min/1.73 m^2).

To calculate the scores from the PAC-SYM subscales (abdominal, rectal, stool), scores for items within a given subscale were summed and divided by the number of items for that subscale.[24]

In the sleep quality analysis, we used only multi-item scales, that is, sleep disturbance, daytime somnolence, sleep adequacy, and summary Sleep Quality. Firstly, correlations of their T scores and the scores from the PAC-SYM subscales were tested using both Kendall (τ-B) and Spearman (ρ) rank correlation coefficients. To assess whether constipation-related symptoms were independently associated with deteriorated overall sleep quality among patients with CKD, we used modified log-Poisson regression models with robust variance (computed with the statsmodels adaptation of the R code published by Gallis and Turner)[25] to estimate the prevalence ratio (PR) of a decreased Sleep Quality score (defined as a T score <40) in patients with CKD.

Each of the gastrointestinal symptoms / disorders that was associated with a higher prevalence of decreased Sleep Quality in univariable analysis (Supplementary material, *Description S1* and *Table S2*) was further analyzed in multivariable analysis to verify the independence of the observed association. To select an optimal set of covariates for multivariable analyses, we performed 2-step variable selection from a wide range of variables that—based on the background knowledge—could be associated with decreased sleep quality (anthropometric and demographic data, diseases, drugs). Firstly, using univariable analyses, we selected all variables that might have been associated with disturbed sleep quality based on the collected data (Vovk–Sellke maximum *P* ratio >1.0; *P* <0.37); they were shown in Supplementary material, *Table S3*. At the next stage, from all selected variables in the previous step, we chose the most informative sets of variables for each domain: to balance goodness-of-fit and model complexity, optimal sets of variables were chosen using Akaike information criterion (Supplementary material, *Description S2*). Finally, multivariable regression models estimating the PR of decreased sleep quality according to each of the selected constipation symptoms, with adjustment for key demographic and clinical data, were performed.

RESULTS

Demographics and comorbidities

Out of 111 patients surveyed in our previous study for gastrointestinal symptoms and HRQOL,[19] 100 patients completed MOS-Sleep-R. Their demographic and clinical characteristics are presented in TABLE 1, and pharmacotherapy is shown in Supplementary material, *Table S1*.

Patients with high eGFR were significantly younger than patients with medium eGFR (adjusted *P* <0.001) and had significantly less severe PAC-SYM stool symptoms than patients with low eGFR levels (adjusted *P* = 0.002). There were less men among patients with medium eGFR than among those with low eGFR (adjusted *P* = 0.03). Patients divided by eGFR terciles seemed to differ with regard to the prevalence of diabetes, functional constipation, and rectal symptoms; however, post hoc tests ceased to be significant after corrections for multiple comparisons (data not shown). Moreover, there were no significant differences between women and men, except for higher frequency of hypothyroidism in women (women, 27.3% vs men, 8.9%; *P* = 0.02).

Sleep quality and its correlation with health-related quality of life

The T scores of the assessed sleep domains did not differ across the eGFR terciles (all *P* >0.05; TABLE 2). Similarly, except for the higher frequency of snoring among men than women (T score median, 44.8 vs 52.4, respectively; *P* = 0.02), no other differences were found between genders. Not surprisingly, Sleep Quality score correlated with all HRQOL domains, with the highest coefficients in vitality and mental health (Supplementary material, *Figure S1*).

Is sleep quality related to symptoms of constipation in patients with chronic kidney disease?

Since in our previous paper we showed several associations between constipation-related symptoms and decreased HRQOL in patients with nondialysis CKD,[19] we performed analyzes to further explore correlations between constipation-related symptoms and subjective sleep quality assessments (TABLE 3). Interestingly, the scores of abdominal and stool scales correlated with all assessed sleep quality domains; the former correlations were stronger and more robust (coefficients have not changed after removal of asymptomatic patients from the analysis, data not shown). Also, less than 7 BMs per week and symptoms of functional constipation were associated with worse sleep quality (TABLE 4). On the contrary, BSFS constipation was not associated with altered sleep quality (all *P* >0.05; TABLE 4). These results were confirmed in a reanalysis using only data of patients not using any laxative drugs (n = 97; data not shown).

Independent factors associated with deteriorated sleep quality among patients with chronic kidney disease

Following analyses from the section above, we explored PAC-SYM items that could be responsible for the observed associations with decreased sleep quality. Based on univariable analyses, we found that abdominal discomfort and pain (PAC-SYM abdominal subscale), too small

TABLE 1 Demographic and clinical parameters of the total study population and according to estimated glomerular filtration rate tercile

Parameter		All	High eGFR tercile	Medium eGFR tercile	Low eGFR tercile	*P* value
Participants, n		100	33	33	34	–
Male sex, n (%)		56 (56)	20 (60.6)	12 (36.4)	24 (70.6)	0.02
Age, y, median (IQR)		68 (55.8–74)	64 (42–70)	71 (68–76)	66.5 (57–75.3)	0.002
BMI, kg/m^2, median (IQR)		28.65 (25.8–30.8)	29.1 (25.5–30.8)	28.6 (26.3–30.5)	28.6 (25.3–31.5)	0.86
eGFR, ml/min/1.73 m^2, median (IQR)		38 (30–47)	57 (47–67)	38 (35–42)	26.5 (17.3–30)	<0.001
Comorbidities, n (%)						
Hypertension		88 (88)	28 (84.8)	31 (93.9)	29 (85.3)	0.44
Diabetes		32 (32)	5 (15.2)	12 (36.4)	15 (44.1)	0.03
Heart failure		19 (19)	3 (9.1)	8 (24.2)	8 (23.5)	0.21
Hypothyroidism		17 (17)	6 (18.2)	6 (18.2)	5 (14.7)	0.91
Depression		4 (4)	0	2 (6.1)	2 (5.9)	0.36
Gastrointestinal symptoms						
PAC-SYM abdominal subscale	≥1 symptom reported, n (%)	59 (59.6)	21 (65.6)	15 (45.5)	23 (67.6)	0.13
	T score, median (IQR)[a]	0.8 (0.5–1.25)	0.5 (0.3–1)	0.8 (0.6–1.3)	0.8 (0.5–1.5)	0.39
	No data, n	1	1	0	0	–
PAC-SYM rectal subscale	≥1 symptom reported, n (%)	30 (30.3)	8 (25)	6 (18.2)	16 (47.1)	0.03
	Score, median (IQR)[a]	0.3 (0.3–1)	0.3 (0.3–0.4)	0.3 (0.3–1.1)	0.7 (0.3–1.3)	0.28
	No data, n	1	1	0	0	–
PAC-SYM stool subscale	≥1 symptom reported, n (%)	69 (69.7)	20 (62.5)	21 (63.6)	28 (82.4)	0.14
	Score, median (IQR)[a]	0.6 (0.2–1)	0.3 (0.2–0.5)	0.6 (0.4–0.8)	0.8 (0.4–1.2)	0.007
	No data, n	1	1	0	0	–
<7 BMs/week	Data available, n (%)	34 (35.4)	8 (24.2)	13 (40.6)	13 (41.9)	0.25
	No data, n	4	0	1	3	–
BSFS	Constipation, n (%)	24 (26.7)	6 (20)	9 (30)	9 (30)	0.6
	No data, n	10	3	3	4	–
Functional constipation, n (%)		19 (19)	3 (9.1)	5 (15.2)	11 (32.4)	0.04

a Only nonzero values were accounted. *P* values were calculated with the Kruskal–Wallis test and the Pearson χ^2 test.

Abbreviations: BMI, body mass index; BMs, bowel movements; BSFS, the Bristol Stool Form Scale; eGFR, estimated glomerular filtration rate; IQR, interquartile range; PAC-SYM, the Patient Assessment of Constipation-Symptoms questionnaire

BMs (PAC-SYM stool subscale), and painful BMs (PAC-SYM rectal subscale) were associated with an increased PR of decreased Sleep Quality (Supplementary material, *Table S2*). Unfortunately, the limited number of participants in the study makes it impossible to clearly determine whether these gastrointestinal symptoms are more often associated with impaired sleep quality in people with impaired versus normal kidney function. It seems, however, that one of these symptoms, abdominal discomfort, can be associated with a higher prevalence of a decreased Sleep Quality score among patients with lower eGFR than those with higher eGFR (Supplementary material, *Figure S2*).

In line with univariable analyzes, functional constipation, defecating less than 7 times a week, as well as presence / severity of abdominal discomfort and pain, as well as too small BMs, remained significantly associated with an increased PR of decreased Sleep Quality, even after adjustment for age, depression, and drugs (TABLE 5 and Supplementary material, *Tables S4–S7*). On the contrary, the association of painful BMs with an increased PR of decreased Sleep Quality ceased to be significant after inclusion of drugs into the model (TABLE 5 and Supplementary material, *Table S8*).

DISCUSSION In the current study using validated questionnaires, we confirmed the associations between sleep problems and constipation-related symptoms in patients with nondialysis CKD. To the best of our knowledge, this is the first study on these associations in patients with CKD. Moreover, according to the objectives of the study, we explored the associations and found a set of symptoms (abdominal discomfort and pain, too small BMs) that are independently associated with the increased PR of lower sleep quality in patients with CKD.

The link between functional gastrointestinal disorders and deteriorated sleep quality has been well documented in non-CKD adult patients. In a population-based study, Wu et al[18] found that excessive daytime sleepiness was significantly associated with an increased odds ratio of diarrhea-predominant irritable bowel syndrome (IBS), alternating IBS, and functional constipation in an

TABLE 2 The results of the Medical Outcomes Study Sleep Scale–Revised across estimated glomerular filtration rate terciles

Variable		All	High eGFR tercile	Medium eGFR tercile	Low eGFR tercile	*P* value
Sleep quality						
T score, median (IQR)		51.88 (43.11–57.5)	53.29 (47.67–57.5)	51.88 (40.66–57.5)	47.67 (40.66–55.74)	0.16[a]
T score <40, n (%)		18 (18)	2 (6.1)	8 (24.2)	8 (23.5)	0.09[b]
Multi-item scales						
Disturbance, T score, median (IQR)		50.96 (42.22–57.2)	52.21 (49.71–57.2)	49.71 (42.22–57.2)	47.21 (37.22–57.2)	0.22[a]
Somnolence, T score, median (IQR)		48.23 (40.52–55.94)	48.23 (44.37–55.94)	48.23 (40.52–52.09)	44.37 (37.62–52.09)	0.2[a]
Adequacy, T score, median (IQR)		57.58 (47.9–62.43)	57.58 (47.9–62.43)	57.58 (47.9–62.43)	52.74 (44.26–61.22)	0.45[a]
Single-item scales						
Shortness of breath	T score, median (IQR)	55.25 (43.47–55.25)	55.25 (43.47–55.25)	55.25 (43.47–55.25)	55.25 (43.47–55.25)	0.76[a]
	"None of the time," n (%)	58 (58)	20 (60.6)	17 (51.5)	21 (61.8)	0.65[b]
Snoring	T score, median (IQR)	44.84 (44.84–52.44)	44.84 (42.94–52.44)	52.44 (44.84–52.44)	44.84 (44.84–52.44)	0.54[a]
	"None of the time," n (%)	20 (20.4)	6 (18.8)	7 (21.2)	7 (21.2)	0.96[b]
	No data, n	2	1	0	1	–
Sleep quantity	Optimal, n (%)	49 (49)	19 (57.6)	17 (51.5)	13 (38.2)	0.27[b]
	Duration, h, median (IQR)	8 (6–8)	8 (7–8)	8 (6–8)	7 (6–8)	0.26[a]

a Kruskal–Wallis test

b χ^2 test

Abbreviations: see **TABLE 1**

TABLE 3 Correlations between the T scores of the Medical Outcomes Study Sleep Scale–Revised (MOS-Sleep-R) and the scale scores of the Patient Assessment of Constipation-Symptoms (PAC-SYM)

MOS-Sleep-R	Correlation coefficient	PAC-SYM score		
		Abdominal symptoms	Rectal symptoms	Stool symptoms
Sleep Quality	Spearman ρ	–0.57 (–0.69 to –0.42)	–0.23 (–0.41 to –0.03)	–0.5 (–0.64 to –0.34)
	P value	<0.001	0.02	<0.001
	Kendall τ B	–0.45 (–0.57 to –0.34)	–0.19 (–0.3 to –0.07)	–0.38 (–0.49 to –0.26)
	P value	<0.001	0.02	<0.001
Sleep disturbance	Spearman ρ	–0.47 (–0.61 to –0.3)	–0.21 (–0.39 to –0.01)	–0.46 (–0.6 to –0.29)
	P value	<0.001	0.04	<0.001
	Kendall τ B	–0.38 (–0.5 to –0.25)	–0.17 (–0.29 to –0.06)	–0.36 (–0.48 to –0.23)
	P value	<0.001	0.04	<0.001
Sleep adequacy	Spearman ρ	–0.43 (–0.58 to –0.25)	–0.17 (–0.36 to 0.03)	–0.28 (–0.45 to –0.09)
	P value	<0.001	0.09	0.005
	Kendall τ B	–0.35 (–0.47 to –0.23)	–0.14 (–0.24 to –0.04)	–0.22 (–0.36 to –0.09)
	P value	<0.001	0.1	0.004
Somnolence	Spearman ρ	–0.39 (–0.54 to –0.21)	–0.08 (–0.28 to 0.12)	–0.39 (–0.55 to –0.21)
	P value	<0.001	0.41	<0.001
	Kendall τ B	–0.3 (–0.42 to –0.18)	–0.07 (–0.19 to 0.05)	–0.31 (–0.44 to –0.18)
	P value	<0.001	0.39	<0.001

adult Chinese population (age, 18–80 years). Interestingly, among French adult patients (mean [SD] age, 48.2 [16.7] years) with functional gastrointestinal disorders, functional constipation and bloating have been associated with insomnia, while functional diarrhea and nonspecific bowel disorders with drowsiness.[17] In our study, insomnia and excessive daytime sleepiness were measured with the MOS-Sleep-R sleep disturbance and somnolence scales, respectively. We found more disturbed sleep in patients with functional constipation and defecating less than 7 times a week, but higher sleepiness only in patients defecating less than 7 times a week. Moreover, the severity of both insomnia and daytime sleepiness correlated with the severity of PAC-SYM abdominal and stool symptoms.

Such strict associations between sleep and gastrointestinal symptoms in patients with CKD emphasize the importance of common risk factors, for example, obesity, depression, melatonin deficiency, or side effects of drugs. Indeed, obesity is an important modifiable risk factor for CKD (via a plethora of mechanisms such as induction

TABLE 4 Differences in the T scores of the Medical Outcomes Study Sleep Scale–Revised between patients with and without constipation

MOS-Sleep-R	Functional constipation		Less than 7 BMs/week		BSFS constipation	
	P value[a]	Difference[b] (95% CI)	*P* value[a]	Difference[b] (95% CI)	*P* value[a]	Difference[b] (95% CI)
Sleep Quality	0.004	–7.02 (–11.23 to –2.8)	<0.001	–7.02 (–11.23 to –2.81)	0.33	–1.88 (–5.62 to 2.8)
Sleep disturbance	0.01	–5.0 (–9.99 to –2.49)	0.003	–5 (–9.99 to –2.5)	0.41	–2.49 (–7.49 to 2.5)
Sleep adequacy	0.19	–4.84 (–9.68 to 0)	<0.001	–4.9 (–9.69 to –4.84)	0.33	–0.01 (–4.85 to 0)
Somnolence	0.09	–3.86 (–11.56 to 0)	0.009	–7.7 (–7.72 to –3.85)	0.86	0.01 (–3.86 to 3.86)

a Groups were compared with the Mann–Whitney test

b Difference between patients with versus without a specific condition presented as the Hodges–Lehmann estimate with 95% CI

Abbreviations: see TABLE 1

TABLE 5 Log-Poisson regression models of a decreased Sleep Quality score prevalence ratio according to constipation-related symptom unadjusted and adjusted for key clinical data

Constipation-related symptom		Univariable analyses, unadjusted		Adjusted model 1[a]		Adjusted model 2[b]	
		PR (95% CI)	*P* value	PR (95% CI)	*P* value	PR (95% CI)	*P* value
Frequency of defecation	7 times/week	Reference	–	Reference	–	Reference	–
	<7 times/week	7.24 (1.74–30.12)	0.007	6.46 (1.55–26.83)	0.01	4.64 (1.13–18.97)	0.03
	>7 times/week	2.93 (0.53–16.19)	0.22	2.55 (0.47–13.91)	0.28	2.3 (0.43–12.41)	0.33
Functional constipation		2.71 (1.21–6.07)	0.02	2.52 (1.15–5.54)	0.02	2.96 (1.36–6.43)	0.006
Abdominal discomfort	Lack	Reference	–	Reference	–	Reference	–
	Mild	4.31 (1.29–14.37)	0.02	3.62 (1.07–12.29)	0.04	3.6 (1.19–10.83)	0.02
	Moderate/severe	7.34 (2.54–21.19)	<0.001	6.83 (2.34–19.95)	< 0.001	7.42 (2.5–21.99)	<0.001
Abdominal pain	Lack	Reference	–	Reference	–	Reference	–
	Mild	4.24 (1.56–11.52)	0.004	3.52 (1.34–9.3)	0.01	2.91 (1.19–7.15)	0.02
	Moderate/severe	7.2 (2.87–18.03)	<0.001	7.98 (3.21–19.85)	<0.001	11.03 (4.82–25.26)	<0.001
Too small BMs	Lack	Reference	–	Reference	–	Reference	–
	Mild	3.34 (1.14–9.82)	0.03	3.12 (1.09–8.96)	0.03	2.97 (1.11–7.94)	0.03
	Moderate/severe	7.6 (3.37–17.16)	<0.001	6.22 (2.51–15.43)	<0.001	5.24 (2.17–12.63)	<0.001
Painful BMs	Lack	Reference	–	Reference	–	Reference	–
	Mild	3.86 (1.69–8.86)	0.001	2.91 (1.13–7.48)	0.03	2.09 (0.84–5.18)	0.11
	Moderate/severe	3.86 (1.26–11.89)	0.02	3.87 (1.11–13.48)	0.03	3.28 (0.89–12.02)	0.07

a Adjusted for age ≥65 and depression

b Adjusted for age ≥65, depression, calcium channel blockers, and diuretics

Abbreviations: PR, prevalence ratio; others, see TABLE 1

of glomerular hyperfiltration, low-grade inflammation, and kidney lipotoxicity),[26,27] obstructive sleep apnea (via both mechanical airway narrowing/collapse and disturbances of airway neuromuscular control),[28] and constipation (via multiple hormones, including excessive endocannabinoid activity and decrease in ghrelin secretion[29]).[16] Also, depression is not only associated with sleep disorders in both nondialysis and dialysis CKD patients[13,30] but is also closely associated with a higher prevalence of constipation in both patients with CKD and the general population.[30,31] Interestingly, while CKD impairs endogenous melatonin synthesis,[15] beneficial effects of melatonin were suggested in the treatment of both specific sleep disorders and IBS with predominant constipation.[32] Moreover, side effects of drugs can underlie the observed coexistence of sleep and gastrointestinal symptoms in patients with CKD. Benzodiazepines, even though they should be avoided in the long-term therapy of insomnia, are frequently used and can cause constipation.[33,34] In our study, calcium channel blockers and diuretics were associated with an increased prevalence of deteriorated sleep quality. It is in agreement with recent studies that have shown that both drug groups are associated with nocturia[35-37] and decreased gastrointestinal motility.[19,38-40] Recent reviews comprehensively analyzed possible pathogenic mechanisms of CKD-related constipation.[41,42]

In this pilot study, we estimated that the prevalence of deteriorated sleep quality in nondialysis CKD patients is higher among those with certain gastrointestinal symptoms (decreased frequency of defecation, functional constipation, abdominal discomfort or pain, too small BMs) even after adjustment for age, depression, and taking drugs.

To elucidate the cause-effect relationship in this complex network of associations, interventional studies (eg, obesity or depression treatment, laxative drugs, melatonin supplementation) recruiting nondialysis CKD patients are needed.

Limitations Limitations of this study include single-center, cross-sectional design, no a priori sample size calculation, and a relatively low number of participants. As a result, we have adjusted the estimated PR of deteriorated sleep quality for some, but not all, possible covariates because inclusion of additional covariates without increasing the number of study participants could result in unreliable, over-fitted models. Even though the MOS-Sleep-R is a validated questionnaire, it cannot be used to diagnose sleep disorders, thus we did not provide associations between gastrointestinal symptoms and specific sleep disorders in patients with CKD.

Conclusions In patients with nondialysis CKD, sleep disorders coexist with constipation-related symptoms. Further studies are needed to fully understand the nature of the observed associations.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

ARTICLE INFORMATION

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CONTRIBUTION STATEMENT JR conceived the concept of the study. JR, ZH, JMW, and ADŚ contributed to the design of the research. JR, ZH, EK, and AT were involved in data collection. JR analyzed the data. ADŚ and JMW coordinated the funding for the project. All authors edited and approved the final version of the manuscript.

CONFLICT OF INTEREST None declared.

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Supplementary material

Ruszkowski J, Heleniak Z, Król E, et al. Associations between symptoms of constipation and sleep quality in patients with nondialysis chronic kidney disease: a cross-sectional study. Pol Arch Intern Med. 2021; 131: 512-519. doi:10.20452/pamw.15974

Table S1. Pharmacotherapy in total study population and according to estimated glomerular filtration rate tercile

	All (n=100)	**High eGFR tercile**	**Medium eGFR tercile**	**Low eGFR tercile**	***P* value**
Beta blockers, n (%)	68	18 (54.5)	24 (72.7)	26 (76.5)	0.12
Calcium channel blockers, n (%)	52	10 (30.3)	19 (57.6)	23 (67.6)	0.007
Diuretics, n (%)	54	15 (45.5)	21 (63.6)	18 (52.9)	0.33
Lactulose, n (%)	3	0	2 (6.1)	1 (2.9)	0.54*
NSAIDs, n (%)	22	6 (18.2)	9 (27.3)	7 (20.6)	0.65
Paracetamol, n (%)	12	1 (3.0)	5 (15.2)	6 (17.6)	0.14*
Calcium supplements, n (%)	18	3 (9.1)	5 (15.2)	10 (29.4)	0.08
Vitamin D, n (%)	30	9 (27.3)	9 (27.3)	12 (35.3)	0.71
Iron, n (%)	7	1 (3.0)	2 (6.1)	4 (11.8)	0.50*
Hypnotics, n (%)	6	1 (3.0)	1 (3.0)	4 (11.8)	0.36*

* Since the assumptions of χ^2-test were violated, Fisher exact probability test was used.

Abbreviations: eGFR: estimated glomerular filtration rate tercile; NSAIDs: nonsteroidal anti-inflammatory drugs

Description S1. Selection of gastrointestinal symptoms significantly associated with altered prevalence ratio of decreased Sleep Quality.

1. Gastrointestinal disorders ($P < 0.05$):

Functional constipation, Frequency of defecation (< 7/week; 7/week; > 7/week).

2. Symptoms treated as binary variables (symptom present or not) ($P < 0.05$):

2.1. Items of the Abdominal Scale:

- abdominal discomfort (≥ 1 point at PAC-SYM Scale);
- abdominal pain (≥ 1 point at PAC-SYM Scale);
- stomach cramps (≥ 1 point at PAC-SYM Scale)

2.2. Items of the Rectal Scale:

- painful bowel movements (≥ 1 point at PAC-SYM Scale);

2.3. Items of the Stool Scale:

- too hard BMs (≥ 1 point at PAC-SYM Scale);
- too small BMs (≥ 1 point at PAC-SYM Scale);
- straining or squeezing (≥ 1 point at PAC-SYM Scale).

3. Symptoms associated with decreased Sleep Quality (2.2.) treated as tri-level variable (Absent / Mild / at least moderate) (at each level $P < 0.05$):

3.1. Items of the Abdominal Scale: abdominal discomfort; abdominal pain;

3.2. Items of the Rectal Scale: painful bowel movements;

3.3. Items of the Stool Scale: too small BMs.

Gastrointestinal disorders and symptoms selected above (section 1. and section 3.) were shown in Table S2.

Table S2. Univariable analyses assessing prevalence ratio of decrease Sleep Quality according to gastrointestinal symptoms and disorders

Variable	Univariable analyses (each row represents separate model)		
	Prevalence ratio	95% CI	*P* value
Abdominal discomfort*	5.86	2.09-16.49	0.001
Abdominal discomfort			
- Lack	reference	-	-
- Mild	4.31	1.29-14.37	0.02
- Moderate/severe	7.34	2.54-21.19	< 0.001
Abdominal pain*	5.33	2.22- 12.79	< 0.001
Abdominal pain:			
- Lack	reference	-	-
- Mild	4.24	1.56-11.52	0.004
- At least medium	7.20	2.87-18.03	< 0.001
Too small BMs*	5.19	2.28-11.85	< 0.001
Too small BMs:			
- Lack	reference	-	-
- Mild	3.34	1.14-9.82	0.03
- At least medium	7.60	3.37-17.16	< 0.001
Painful BMs*	3.86	1.81-8.27	< 0.001
Painful BMs:			
- Lack	reference	-	-
- Mild	3.86	1.69-8.86	0.001
- Moderate/severe	3.86	1.26-11.89	0.02
Defecation frequency			
- 7 times a week	reference	-	-
- < 7 times a week	7.23	1.74-30.12	0.007
- > 7 times a week	2.93	0.53-16.19	0.22
Functional constipation	2.71	1.21-6.07	0.02

* ≥1 point at PAC-SYM Scale

Abbreviations: BMs: bowel movements; PAC-SYM: the Patient Assessment of Constipation-Symptoms questionnaire

Table S3. Univariable analyses assessing prevalence ratio of decrease Sleep Quality [T Score < 40]

Variable	Univariable analyses (each row represents separate model)		
	Prevalence ratio	95% CI	*P* value
Gender:			
- male	reference	-	-
- female	1.59	0.69-3.69	0.28
Age ≥ 65	1.66	0.64-4.30	0.29
eGFR tercile			
- high	reference	-	-
- medium	4.00	0.92-17.44	0.07
- low	3.88	0.89-16.95	0.07
Depression	4.80	2.31-9.98	< 0.001
Use of beta-blockers	1.65	0.59-4.61	0.34
Use of CCBs	3.23	1.14-9.13	0.03
Use of diuretics	2.21	0.85-5.75	0.10
Use of hypnotics	1.96	0.58- 6.61	0.28
Use of NSAIDs	1.77	0.75-4.18	0.19

Variables with Vovk-Sellke maximum *P*-ratio > 1.0, i.e. $P < 0.37$, were shown.

Abbreviations: CCBs: calcium channel blockers; NSAIDs: nonsteroidal anti-inflammatory drugs

Description S2. Selection of optimal set of variables at each domain based on minimal Akaike information criterion (AIC).

Variables shown in Table S3 were categorized based on the domain. Then, optimal set of variables (1-item set were permitted) at each domain were selected based on the minimum value of the Akaike information criterion. Below, the results were shown:

a. Anthropometric and demographic data: age ≥ 65
b. Disease: depression (AIC 97.41)
c. Drugs: Ca channel blockers and diuretics (AIC 96.59)

Table S4. Log-Poisson regression models of decreased Sleep Quality Score prevalence ratio according to defecation frequency adjusted for key clinical data

Variable	Model adjusted for age		Model adjusted for age, depression		Model adjusted for age, depression and drugs	
	PR (95% CI)	*P* value	PR (95% CI)	*P* value	PR (95% CI)	*P* value
Defecation frequency						
- 7 times a week	reference	-	Reference	-	Reference	-
- < 7 times a week	7.43 (1.82-30.32)	0.005	6.46 (1.55-26.83)	0.01	4.64 (1.13-18.97)	0.03
- > 7 times a week	3.21 (0.59-17.247)	0.17	2.55 (0.47-13.90)	0.28	2.30 (0.43-12.41)	0.33
Age ≥ 65	2.12 (0.80-5.66)	0.13	2.24 (0.937-5.35)	0.07	1.99 (0.86-4.61)	0.11
Depression	-	-	3.83 (1.67-8.78)	0.002	3.11 (1.32-7.31)	0.009
Use of CCBs	-	-	-	-	1.92 (0.68-5.40)	0.22
Use of diuretics	-	-	-	-	1.66 (0.60-4.64)	0.33

Abbreviations: CCBs: calcium channel blockers; PR: prevalence ratio.

Table S5. Log-Poisson regression models of decreased Sleep Quality Score prevalence ratio according to abdominal discomfort adjusted for key clinical data

Variable	Model adjusted for age		Model adjusted for age, depression		Model adjusted for age, depression and drugs	
	PR (95% CI)	*P* value	PR (95% CI)	*P* value	PR (95% CI)	*P* value
Abdominal discomfort						
- Lack	reference	-	reference	-	reference	-
- Mild	4.49 (1.39-14.52)	0.01	3.62 (1.07-12.29)	0.04	3.60 (1.19-10.83)	0.02
- Moderate/severe	7.55 (2.60-21.92)	< 0.001	6.83 (2.34-19.95)	< 0.001	7.42 (2.50-21.99)	< 0.001
Age ≥ 65	1.86 (0.79-4.39)	0.16	2.08 (0.93-4.64)	0.08	2.03 (0.96-4.26)	0.06
Depression	-	-	2.72 (1.22-6.07)	0.02	2.02 (1.12-3.64)	0.02
Use of CCBs	-	-	-	-	3.10 (1.15-8.37)	0.03
Use of diuretics	-	-	-	-	1.76 (0.86-3.59)	0.12

Abbreviations: CCBs: calcium channel blockers; PR: prevalence ratio.

Table S6. Log-Poisson regression models of decreased Sleep Quality Score prevalence ratio according to abdominal pain adjusted for key clinical data

Variable	Model adjusted for age		Model adjusted for age, depression		Model adjusted for age, depression and drugs	
	PR (95% CI)	*P* value	PR (95% CI)	*P* value	PR (95% CI)	*P* value
Abdominal pain:						
- Lack	Reference	-	reference	-	Reference	-
- Mild	4.17 (1.57-11.09)	0.004	3.52 (1.34-9.30)	0.01	2.91 (1.19-7.15)	0.02
- At least medium	8.47 (3.39-21.14)	< 0.001	7.98 (3.21-19.85)	< 0.001	11.04 (4.82-25.26)	< 0.001
Age ≥ 65	2.14 (1.00-4.60)	0.05	2.51 (1.26-4.98)	0.009	2.87 (1.31-6.25)	0.008
Depression	-	-	3.18 (1.70-5.93)	< 0.001	1.93 (0.85-4.42)	0.12
Use of CCBs	-	-	-	-	2.86 (1.07-7.67)	0.04
Use of diuretics	-	-	-	-	2.17 (0.91-5.16)	0.08

Abbreviations: CCBs: calcium channel blockers; PR: prevalence ratio.

Table S7. Log-Poisson regression models of decreased Sleep Quality Score prevalence ratio according to too small bowel movement adjusted for key clinical data

Variable	Model adjusted for age		Model adjusted for age, depression		Model adjusted for age, depression and drugs	
	PR (95% CI)	*P* value	PR (95% CI)	*P* value	PR (95% CI)	*P* value
Too small BMs:						
- Lack	Reference	-	Reference	-	Reference	-
- Mild	3.36 (1.15-9.85)	0.03	3.12 (1.09-8.96)	0.03	2.97 (1.11-7.94)	0.03
- At least medium	7.25 (3.11-16.89)	< 0.001	6.22 (2.51-15.43)	< 0.001	5.24 (2.17-12.63)	< 0.001
Age ≥ 65	1.16 (0.46-2.97)	0.75	1.24 (0.48-3.21)	0.65	1.02 (0.40-2.57)	0.97
Depression	-	-	2.98 (1.23-7.24)	0.02	2.36 (0.98-5.67)	0.05
Use of CCBs	-	-	-	-	2.06 (0.74-5.70)	0.17
Use of diuretics	-	-	-	-	1.83 (0.86-3.88)	0.12

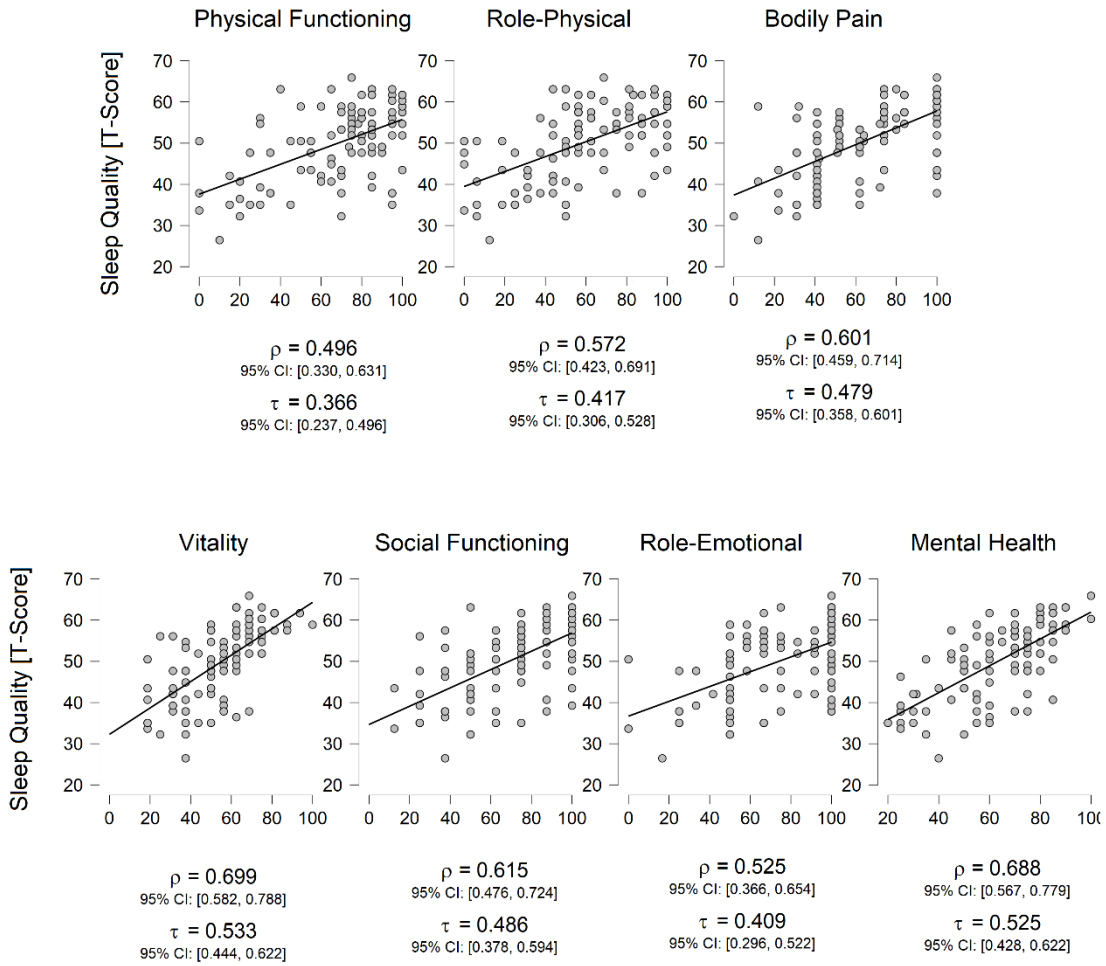
Abbreviations: BMs: bowel movements; CCBs: calcium channel blockers; PR: prevalence ratio.

Table S8. Log-Poisson regression models of decreased Sleep Quality Score prevalence ratio according to painful bowel movement adjusted for key clinical data

Variable	Model adjusted for age		Model adjusted for age, depression		Model adjusted for age, depression and drugs	
	PR (95% CI)	***P* value**	**PR (95% CI)**	***P* value**	**PR (95% CI)**	***P* value**
Painful BMs						
- Lack	Reference	-	Reference	-	Reference	-
- Mild	3.68 (1.53-8.89)	0.004	2.91 (1.13-7.47)	0.03	2.09 (0.84-5.18)	0.11
- Moderate/severe	4.84 (1.32-17.75)	0.02	3.87 (1.11-13.48)	0.03	3.28 (0.89-12.02)	0.07
Age ≥ 65	1.84 (0.77-4.43)	0.17	2.03 (0.86-4.75)	0.11	1.96 (0.75-5.14)	0.17
Depression	-	-	2.63 (1.15-6.00)	0.02	2.31 (0.97-5.53)	0.06
Use of CCBs	-	-	-	-	2.38 (0.79-7.13)	0.12
Use of diuretics	-	-	-	-	1.54 (0.62-3.86)	0.35

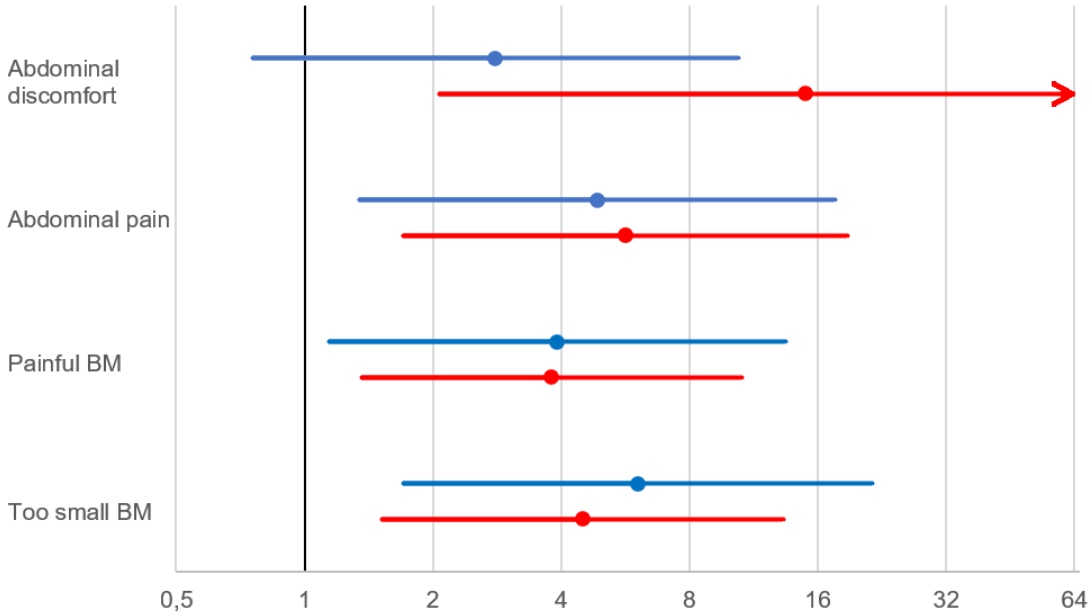
Abbreviations: BMs: bowel movements; CCBs: calcium channel blockers; PR: prevalence ratio.

Figure S1. Correlations between Sleep Quality T Score and SF-36v2 domains



Below each scatter plot, Spearman's ρ and Kendall's τ-B with 95% confidence intervals were shown.

Figure S2. Prevalence ratio of deteriorated Sleep Quality in patients with according to gastrointestinal symptoms and estimated glomerular filtration rate



Dots: estimated prevalence ratio (PR).
Lines: 95% confidence interval (CI).

Blue: patients with eGFR >= median (38 ml/min/1.73m^2);
Red: patients with eGFR < median (38 ml/min/1.73m^2).

Upper range of 95% CI for patients with abdominal discomfort and eGFR < median was not shown (= 108.81)

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Systematic Review

Prevalence and Severity of Lower Gastrointestinal Symptoms amongst Non-Dialysis Chronic Kidney Disease Patients: A Systematic Review and Meta-Analysis

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Abstract: Chronic kidney disease (CKD) patients experience a wide range of symptoms that deteriorate their health-related quality of life (HRQoL). We aimed to estimate the prevalence and severity of lower gastrointestinal (GI) symptoms in non-dialysis CKD adult outpatients, and to summarize the relationships between these symptoms and HRQoL, laboratory test results, and clinical data. The protocol of the study was preregistered (PROSPERO CRD42021255122). We searched MEDLINE, Scopus, Web of Science, and grey literature sources from the databases' inception up until 27 November 2021. Wide citation chasing was conducted. Single proportions (prevalence of functional constipation, self-reported constipation, diarrhea, abdominal bloating, fecal incontinence, and abdominal/rectal pain) were pooled using generalized linear mixed models. A total of 37 studies with 12,074 patients were included. We found that lower GI symptoms, especially self-reported abdominal bloating [CKD G1–2: 48.45% (95% CI: 43.5–53.4%; 2 studies); G3: 46.95% (95% CI: 45.0–48.9%; 2 studies), G4–5: 36.1% (95% CI: 25.4–48.5%; 8 studies)] and constipation [CKD G1–2: 31.8% (95% CI: 13.9–54.9%); G3: 29.8% (95% CI: 21.2–40.1%; 4 studies); G4–5: 38.8% (95% CI: 30.9–47.4%); 22 studies)], were common in non-dialysis CKD patients. The severity of the symptoms was limited. Self-reported constipation was most consistently associated with worse HRQoL, whereas hard stool consistency was associated with higher uremic toxins levels. To conclude, since lower GI symptoms are common in CKD, using symptom questionnaires that do not take them into account cannot provide full insight into the patient's experience. Further studies are needed to cover identified knowledge gaps, including the exploration of the pathophysiology of GI symptoms in CKD with multi-omics data.

Keywords: conservative management; digestive symptoms; symptomatology

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1. Introduction

Chronic kidney disease (CKD), defined as abnormalities of kidney structure or function present for ≥3 months, with implications for health, is a common condition affecting ca. 9.1% of the global population [1]. A decline in kidney function disrupts several physiological processes and adversely affects multiple organs [2]. Therefore, CKD patients suffer from such conditions as anemia, cardiovascular disease, immune dysfunction, malnutrition, mineral and bone disorder, and water–electrolyte imbalance [2]. As a consequence, CKD patients experience a wide range of symptoms that deteriorate both their physical and mental health-related quality of life (HRQoL) [3,4]. The overall burden of CKD is substantial; it is estimated that CKD leads to a loss of 451.3 years of full health per 100,000 population due to premature mortality or disability (age-standardized disability-adjusted life year (DALY) rate) and is the 12th leading cause of death out of 133 conditions with an estimated

2.6 million deaths in total in 2017 [1]. Increased cardiovascular mortality in CKD is an essential contributor to these appalling statistics [1,2].

Among a plethora of CKD symptoms, lower gastrointestinal (GI) ones are gaining more and more attention in recent years. This is especially true for constipation [5]. Recent epidemiological registry-based studies revealed that constipation is associated with higher incidence rates of CKD and kidney failure [6,7]. Surprisingly, how CKD progression affects the lower GI symptom burden has not yet been systematically studied. Intuitively, as CKD progresses, both the prevalence and severity of GI symptoms should increase. This is a crucial consideration, as several GI symptoms were found to be associated with deteriorated HRQoL in both the general and CKD populations [8,9].

While there are systematic reviews assessing the prevalence of several symptoms in CKD patients [3,10], none are dedicated to a comprehensive analysis of lower GI symptoms in non-dialysis-dependent patients. This patient population deserves special attention because they constitute more than 99% of all CKD patients [1]; moreover, non-dialyzed CKD patients may have different risk factors and implications of GI symptoms than patients undergoing renal replacement therapy [10]. Because patients can understand symptoms differently than health practitioners, a careful approach is required to estimate the prevalence and implications of each from the spectrum of GI symptoms [11,12].

The primary objective of the review was to estimate the prevalence and severity of lower GI symptoms in non-dialysis CKD patients worldwide. Additionally, we aimed to identify the relationships between these symptoms and HRQoL, laboratory test results, and clinical data.

2. Materials and Methods

A protocol for this systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO 2021 CRD42021255122). All deviations from the protocol were listed and explained in Table S1. The article was written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA 2020) statement [13].

2.1. Eligibility Criteria

We aimed to include all observational studies reporting at least one of the predefined outcomes and recruiting adult outpatients with CKD that were treated without dialysis. There were no language restrictions, nor did we exclude studies based on the date of publication or sample size. We specified and explained the eligibility criteria in Supplementary Materials, Methods S1. In this article, we show data on patients that did not receive kidney transplants; articles regarding patients after kidney transplantation will be reviewed in a separate article.

2.2. Information Sources and Search Strategy

To identify the studies of interest, we systematically searched MEDLINE (via PubMed), Scopus, Web of Science Core Collection, Korean Journal Database (via Web of Science), and SciELO (via Web of Science). The databases were searched from inception, and all languages were considered. The initial search was performed on 24 May 2021, and it was rerun on 27 November 2021. Additional searches of the database Open Dissertations (via EBSCO; on 24 May 2021 and 27 November 2021) and American Society of Nephrology conference abstracts from the last ten years (ASN Kidney Week 2011–2021) were conducted.

Literature search strategies consisted of two parts: the first dedicated to finding articles about populations of interest, and the second dedicated to the outcomes of interest. To realize the first aim, we modified the high-sensitivity CKD filter developed by Iansavichus et al. [14] (removal of elements referring to dialysis and hyperphosphatemia). To find studies reporting the outcomes, we used medical subject headings (MeSH) or other subject terms, keywords, and synonyms related to outcomes of interest. Full search strategies for each of the databases were shown in the Table S2.

The CitationChaser Shiny app. [15] was used to perform forward citation chasing of articles presenting symptom questionnaires of interest on 14 November and 26 December 2021 (Table S3). Finally, we used the CitationChaser Shiny app. [15] also for both backward and forward citation chasing of the included studies on 22 January 2022.

2.3. Study Selection, and Data Collection Process

All search results were imported into the Rayyan QCRI reference manager web application for deduplication and screening [16]. JR excluded duplicates. Two investigators (Ruszkowski, J and either Majkutewicz, K or Heleniak, Z) independently screened all article titles and abstracts for eligibility (blind mode). Full texts of the articles that fulfilled the initial screening criteria were acquired and reviewed for subsequent inclusion, against the eligibility criteria.

Data were independently extracted by two authors (Ruszkowski, J and either Majkutewicz, K or Heleniak, Z) in a blinded standardized manner using the Systematic Review Data Repository Plus (SRDR+; https://srdrplus.ahrq.gov (accessed on 18 September 2022)). Items of electronic extraction form are listed in Table S4. All the differences were settled by discussion between all researchers. Both main manuscripts and all available supplementary materials of the included studies were evaluated. If the outcome was measured at multiple time points, we extracted data from the first measurement. In the case of missing crucial data, we tried to contact authors via e-mail or ResearchGate. Ruszkowski, J exported data from SRDR+ as an xlsx file and processed data using both Pandas 1.3.5 [17] and manually (Excel, Microsoft Office 365 (Redmond, WA, USA)).

2.4. Study Risk of Bias and Reporting Bias Assessment

Two reviewers (Ruszkowski, J and either Majkutewicz, K or Heleniak, Z) assessed the quality of all included studies using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Prevalence Studies [18]. Assessment of "reporting biases" (e.g., publication bias) are described in Supplementary Materials, Methods S2.

2.5. Synthesis Methods and Certainty Assessment

Since the burden of disease- and treatment-related symptoms increases with the progression of CKD [19], we decided to meta-analyze all outcomes separately in the subgroups as follows: early CKD (G1 and G2, i.e., estimated glomerular filtration rate (eGFR) $\geq$ 60 mL/min per 1.73 m^2), moderate CKD (G3, i.e., eGFR 30–59 mL/min/1.73 m^2), and advanced CKD (G4 and G5, i.e., eGFR < 30 mL/min/1.73 m^2). We planned to conduct separate meta-analyses according to albuminuria categories; however, data on albuminuria were not reported in the included studies. Location of data collection (countries) were grouped into six World Health Organization (WHO) regions.

Prevalence and severity data were synthesized when available from at least 2 studies. Results for each prevalence outcome expressed as single proportions were pooled using generalized linear mixed models (GLMM). Specifically, the mean prevalence across subsets of studies was estimated with a random intercept logistic regression model (logit transformation) via the maximum-likelihood approach using the *metaprop* function from the 'meta' package (version 5.2-0) [20]. If at least 3 studies were available for a specific outcome–population pair, a 95% prediction interval (95% PI) for the proportion in a new study was calculated. To calculate 95% PI, 'meta' uses the *t*-distribution with $(n - 2)$ degrees of freedom where n corresponds to the number of studies in the meta-analysis [20,21]. To compare the prevalence between subgroups, a meta-analysis of within-study odds ratios was conducted using a random effects model with a restricted maximum-likelihood (REML) estimator for τ^2.

Since data on severity were collected as ordered discrete variables (e.g., "mild", "severe", "overwhelming") that can be perceived as more informative for the larger audience than a continuous estimator of severity, we preferred to meta-analyze the prevalence of each category of severity (multi-category prevalence [22]). It was performed using a MetaXL

implementation of a random-effects meta-analysis with the Freeman–Tukey double arcsine transformation of proportions with the DerSimonian and Laird estimator of variance (it is the only available estimator) [22]. The same method was used to meta-analyze data on the number of bowel movements (BMs) per week, because it was reported in studies as categorical data (less than 3; at least 3 but less than 7; more than 7). Alternatively, if severity was available only as a continuous variable, a random-effects meta-analysis of single means was planned to be conducted.

The results for prevalence data (proportions) were multiplied by 100% to be interpretable as a percentage of the population. Forest plots were generated using the *forest* function from the 'meta' package [20]. Associations/correlations between each of the lower GI symptoms/syndromes and HRQoL/laboratory test results/clinical data were presented via the structured tabulation of results across studies and discussed. The meta-analyses of such associations/correlations were not planned, nor performed.

Confidence interval calculation, subgroup analysis, sensitivity analysis, and certainty assessment are detailed in Supplementary Materials, Methods S3.

3. Results

3.1. Study Selection

Figure 1 shows the study selection process. We found 14,730 records through database searching. After duplicates removal and records screening, we reviewed 165 full-text documents and included 27 reports of 24 studies. We identified an additional 6834 records using citation chasing of both included studies and articles introducing selected questionnaires; after reviewing 118 full-text documents, we included 17 papers. Additionally, we added five papers manually. We listed reasons for exclusion in Table S5. Taken together, we included 49 reports of 37 studies in our systematic review. Moreover, 25 records are pending for inclusion in our future systematic review dedicated to the same outcomes in patients after kidney transplantation.

3.2. Study Characteristics and Risk of Bias

Basic characteristics of the included studies are summarized in Table 1. All except seven studies had a cross-sectional design: five were prospective cohorts [23–27], one a retrospective cohort [28], and one was a case-control study [29]. There were studies from each of the WHO regions: 12 from the Western Pacific Region (Australia, Brunei, China, Japan, Malaysia, and South Korea), 11 from the European Region (Belgium, Denmark, Germany, Italy, the Netherlands, Poland, Spain, Sweden, Turkey, and the United Kingdom), 6 from the Region of the Americas (Brazil, Mexico, United States), 4 from the South-East Asian Region (all from Sri Lanka), 2 from the African Region (both from Nigeria), and 2 from the Eastern Mediterranean Region (Iraq, Saudi Arabia). Besides reports written in English, there were 4 studies reported in other languages (German [30], Spanish [27,28,31]).

The vast majority of studies reported data collected in CKD G4–5 patients (30 studies), whereas far fewer studies reported data on GI symptomatology in the early stages of CKD (6 in G1–2 [9,32–36]; 10 in G3 [9,32–40]). Subgroup characteristics were described in Supplementary Materials, Results S1.

The sample frame was poorly described, questionable, or clearly inappropriate to address the target general CKD population in 25 (68%) studies. Since the objectives of individual studies varied from ours, the studies used too-restrictive inclusion criteria (e.g., only CKD G5 patients receiving palliative treatment) or too-wide exclusion criteria (e.g., suffering from diabetes mellitus or heart failure, or using such drugs as beta-blockers and tricyclic antidepressants [29]; exclusion criteria of all studies are listed in Table S6) to obtain a representative CKD population. Moreover, participants were recruited in a recommended way in only 13 (35%) studies; other studies used convenience sampling or did not clearly report the method of sampling. The sample size was judged as adequate in only 6 (16%) studies. All of these limitations in the included studies may increase the risk of bias in the observed results. On the other hand, the risk of measurement/classification bias was

limited: 24 (65%) studies used validated questionnaires to collect data on GI symptoms, and 20 (54%) studies collected data in a standard, reliable way for all participants (the reliability of data collection in the next 15 studies was unclear, not necessarily low). The full risk of bias assessment is shown in Table S7.

Table 1. Included studies.

Author, Reference	Extracted Populations			Outcomes	Study Design	Country	Study Period
	CKD Stage (N)	Age	Male (%)				
Gordon, S.J.; et al. [41]	G4–5 (4)	50	75.0%	D [a]	cross-sectional	USA	(1976)
Yapa, H.E.; et al. [39]	G3b (224) G4–5 (443)	55.96 61.34	60.7% 65.5%	C, C-s, D, D-s	cross-sectional	Sri Lanka	2018–2019
Muhd Ariffin, N.F.; et al. [42]	G5 (50)	NR	NR	C, AP, B, D	cross-sectional	Brunei	(2016)
Ramos, C.I.; et al. [40]	G3 (6) G4–5 (36)	55.83 59.58	83.3% 52.8%	BSFS, FC	cross-sectional	Brazil	2015–2016
Trimingham, C.; et al. [12]	General population of non-dialysis CKD patients (95)	NR	47.4%	BSFS, AP, B, BM	cross-sectional	Australia	(2018)
Sanya, E.O. and Ogunniyi, A. [43]	General population of non-dialysis CKD patients (60)	39	NR	C, D	cross-sectional	Nigeria	2000–2000
Saini, T.; et al. [44]	G4–5 (11)	67	72.7%	C, B, D	cross-sectional	UK	2005–2005
Ohkuma, T.; et al. [45]	General population of non-dialysis patients with diabetic kidney disease (2245)	NR	NR	BM	cross-sectional	Japan	2008–2010
Ruszkowski, J.; et al. [9,46]	G1–2 (16) G3 (69) G4–5 (26)	49.6 66.8 63.5	37.5% 52.2% 76.9%	BSFS, FC, AP, AP-s, B, B-s, BM	cross-sectional	Poland	2018–2019
Quintal-Medina, I.A.; et al. [27]	G5 (70)	59	55.7%	C, C-s, D, D-s	prospective cohort	Mexico	2018–2018
Meade, A.; et al. [47]	G4–5 (134)	64.6	64.9%	BSFS, B, BM, RP, FI	cross-sectional	Australia	2017–2018
Wizemann, V. and Benz, U. [30]	G5 (20)	NR	NR	C, AP, B, D	cross-sectional	Germany	(1978)
Zhang, X.; et al. [32]	G1–2 (370) G3 (2541) G4–5 (688)	51.6 59.2 58.8	57.0% 56.7% 47.8%	B	cross-sectional	USA	2003–2008
Gryp, T.; et al. [33,48]	G1–2 (37) G3 (44) G4–5 (33)	51.3 64 69.5	54.05% 65.9% 72.7%	BSFS	cross-sectional	Belgium	(2020)
Miskulin, D.C. and the HALT-PKD studies investigators [49,50]	ADPKD G1–4 (1043)	41.8	50.1%	AP, AP-s	cross-sectional	USA	2006–2009
Windahl, K. and the EQUAL study inves-tigators [23,51–53]	G4–5 (1205)	76 [b]	64.6% [b]	C, D, C-s, D-s	prospective cohort	Germany, Italy, the Netherlands, Poland, Sweden, UK	2012–2018

Table 1. *Cont.*

Author, Reference	Extracted Populations			Outcomes	Study Design	Country	Study Period
	CKD Stage (N)	Age	Male (%)				
Ducharlet, K.; et al. [24]	G4 (31)	71	74%	C, D, C-s, D-s	prospective cohort	Australia	2014–2014
Grove, B.E.; et al. [38]	G3 (141) G4–5 (92)	65 68	63.1% 72.8%	C, D, C-s, D-s	cross-sectional	Denmark	2019–2019
Onodugo, O.D.; et al. [54]	G5 (80)	41.5	48.8%	C [a], D [a]	cross-sectional	Nigeria	2015–2015
Allawi, A.A. [29]	G5 (35)	55.4	62.9%	C	case-control	Iraq	2016–2016
Lee, A.; et al. [55]	G5 (21)	64.2	47.6%	C, BSFS, FC	cross-sectional	Australia	(2016)
Dawson, J.; et al. [37]	G3 (8) G4–5 (92)	80.6 82.4	75% 64.1%	C, D, C-s, D-s	cross-sectional	Australia	2016–2019
Abeywickrama, H.M.; et al. [34]	G1–2 (2) G3 (45) G4–5 (73)	66 60.5 62.6	100% 73.3% 65.8%	D, D-s	cross-sectional	Sri Lanka	2019–2019
Lee, S.J. and Jeon, J.H. [35]	G1–2 (22) G3 (83) G4–5 (38)	61.7 68.8 63.7	95.5% 62.7% 42.1%	C, C-s, D, D-s	cross-sectional	South Korea	2013–2013
Yong, D.S.P.; et al. [56]	G5 (45)	73.1	46.7%	C, C-s, B, B-s	cross-sectional	China	2006–2007
Senanayake, S.; et al. [36]	G1–2 (96) G3 (163) G4–5 (782)	52.5 57.9 59.7	32.3% 51.5% 68.3%	D, D-s	cross-sectional	Sri Lanka	2016–2016
Abdel-Kader, K.; et al. [57]	G4–5 (87)	51	65.5%	C, C-s, D, D-s	cross-sectional	USA	2004–2006
Wan Zukiman, W.Z.H.; et al. [58]	G5 (100)	61.0	48%	C, C-s, D, D-s	cross-sectional	Malaysia	2015–2016
Gutiérrez Sánchez, D.; et al. [31,59–61]	G4–5 (124)	69.8	70.2%	C, C-s, D, D-s	cross-sectional	Spain	2015–2015
Murtagh, F.E.; et al. [62,63]	G5 (66)	82	48.5%	C, C-s, B, B-s, D, D-s	cross-sectional	England	2005–2006
Turkmen, K.; et al. [25]	Fabry nephropathy (11)	41.3	63.6%	AP	prospective cohort	Turkey	2014–2016
Brennan, F.; et al. [64]	G5 (42)	83	42.9%	C, C-s, D, D-s	cross-sectional	Australia	2010–2012
Murphy, E.L.; et al. [65]	G4–5 (55)	82	47.3%	C, C-s, D, D-s	cross-sectional	UK	2005–2006
Taira, K.; et al. [66]	General population of non-dialysis CKD patients (15)	54.9	73.3%	C, D	cross-sectional	Sri Lanka	2015–2015
Purtell, L.; et al. [26,67]	G4–5 (46)	78.3	39.1%	C, C-s, D, D-s	prospective cohort	Australia	2016–2017
de Miguel, C.; et al. [28]	G4–5 (102)	79.6	59.8%	C	retrospective cohort	Spain	1997–2009
Almutary, H.; et al. [68,69]	G4–5 (107)	51.6	55.1%	C, C-s, D, D-s	cross-sectional	Saudi Arabia	2013–2014

[a] only clinical/lab/HRQoL associations with the outcome were extracted, not the prevalence or severity. [b] The median age and percentage of males in the EQUAL study were extracted from the article written by Windahl et al. [23], whereas the number of analyzed participants was larger (data from the authors). Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; AP, self-reported abdominal pain; B, self-reported bloating; BM, frequency of bowel movements; BMI, body mass index; BSFS, stool consistency according to the Bristol stool form scale; C, self-reported constipation; D, self-reported diarrhea; FC, functional constipation; FI, self-reported fecal incontinence; NR, not reported; RP, rectal pain; -s, severity of the symptom.

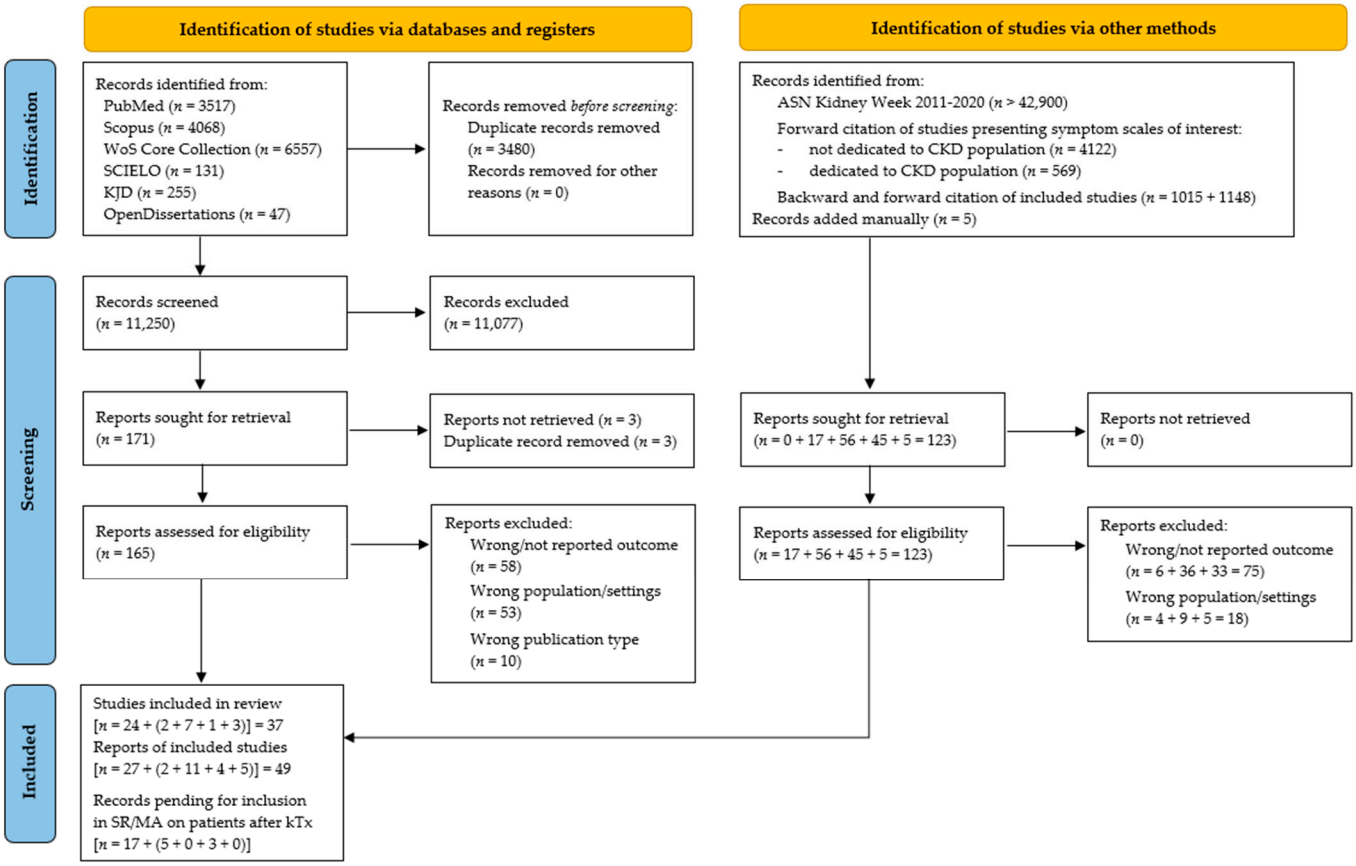

Figure 1. PRISMA 2020 flow diagram.

3.3. Constipation: Prevalence and Severity

3.3.1. Self-Reported Constipation

Data on self-reported constipation prevalence in CKD were provided in 24 studies, of which 22 were included in the meta-analyses below (Figure 2). They were conducted primarily in the WHO Western Pacific (9 studies [24,26,35,37,42,55,56,58,64]) and European (8 studies [23,28,30,31,38,44,53,62,65]) Regions. Data were collected using authors' questionnaires/during anamnesis in the case of 8 studies, and using validated questionnaires: renal version of the Patient Outcome Scale—symptom module (POS-S Renal; 5 studies [24,27,31,35,64]); Integrated Palliative Care Outcome Scale (IPOS)-Renal (3 studies [26,37,39]); Dialysis Symptom Index (DSI) (3 studies [23,53,57,58]); Memorial Symptom Assessment Scale–Short Form (MSAS-SF; 2 studies [44,62]).

Only one study reported self-reported constipation prevalence among patients with CKD G1–G2 (31.8%, 95% CI: 13.9–54.9%); therefore, a meta-analysis was not performed for this subgroup [35]. Based on 7 patients reporting constipation in this subgroup, it was estimated that 57.1% (95% CI: 28.6–91.5%) experienced mild, 28.6% (95% CI: 0–62.9%) moderate, 14.3% (95% CI: 0–48.6%) severe, and 0% (95% CI: 0–34.3%) overwhelming severity [35].

A total of 4 studies were included in the prevalence analysis for the CKD G3 subgroup [35,37–39]. The observed prevalence ranged from 13 to 43% mainly due to between-study variance ($\tau^2 = 0.13$; $I^2 = 77\%$). The estimated average prevalence was 29.8% (95% CI: 21.2–40.1%). The 95% prediction interval (PI) for the prevalence in new studies ranged from 6.2 to 73.1%. Three studies presented data that could be meta-analyzed for the symptom severity (Table S8). Mild, moderate, severe, and overwhelming severity of constipation was, on average, reported by 37.6% (95% CI: 10.4–69.1%), 40.9% (95% CI: 12.8–72.2%), 15.8% (0–41.2%), and 5.6% (0–23.9%) of patients reporting the symptom, respectively.

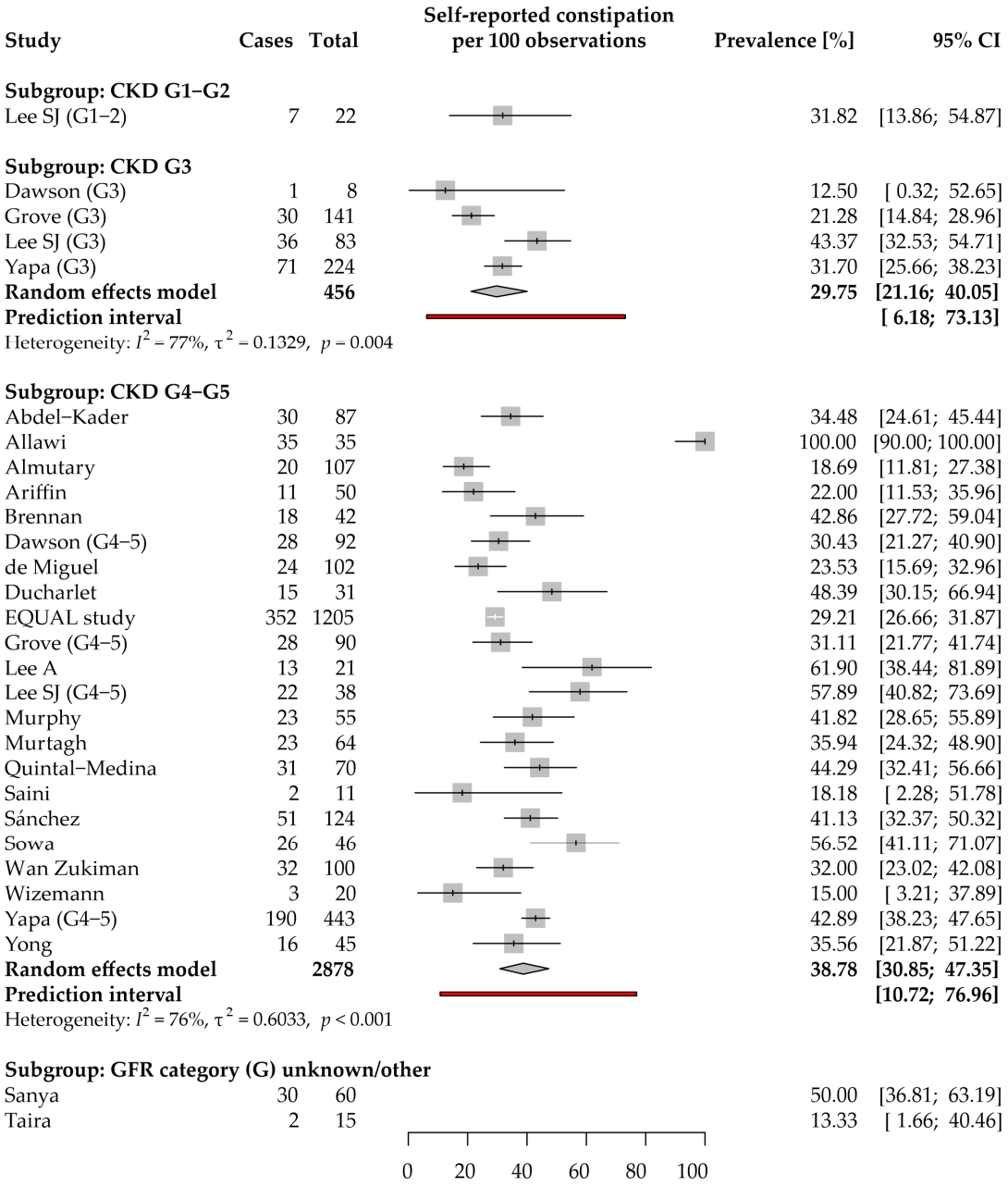

Figure 2. Forest plot with pooled point prevalence estimates for self-reported constipation in chronic kidney disease by stages.

A total of 22 studies enrolling 2878 patients were included in the analysis for the CKD G4–5 subgroup [24,26–31,35,37–39,42,44,53,55–58,62,64–66]. The observed prevalence ranged from 15 up to 100%. The estimated average prevalence was 38.8% (95% CI: 30.9–47.4%). Observed heterogeneity in the reported results came from the substantial between-study variance (τ^2 = 0.60; I^2 = 76%) rather than sampling. A subgroup analysis revealed that it may have partially resulted from the difference in the location of data collection (p = 0.02); studies conducted in the European Region (31.4%; 95% CI: 26.8–36.5%) tended to report a lower prevalence than studies from the Western Pacific or American WHO Regions (Table S9). Neither study period, mean age of participants, nor sex of participants were significantly associated with the reported prevalence. While there was no clear asymmetry in the funnel plot (Peters' regression test: p = 0.22), an analysis of both the Doi plot and the LFK index suggested a minor bias favoring publication of studies with a higher prevalence of self-reported constipation in CKD G4–5 (Figure S1). The 95% PI for the prevalence

in new studies ranged from 10.7 to 77.0%. Based on four studies that simultaneously reported the prevalence in both CKD G3 and G4–5 stages, self-reported constipation was more likely to be reported in CKD G4–5 subgroups than in G3 subgroups (odds ratio, OR: 1.67 [95% CI: 1.27–2.19], $p < 0.001$). It cannot be explained by the difference in the mean age of patients ($p = 0.78$; Figures S2 and S3). Eight studies with 360 patients reporting constipation were included in the meta-analysis of severity (Table S8). Mild, moderate, severe, and overwhelming severity of constipation was, on average, reported by 43.8% (95% CI: 32.8–54.4%), 34.4% (95% CI: 24.2–44.9%), 18.2% (10.3–27.2%), and 3.6% (0.4–9.0%) of patients reporting the symptom, respectively. A small part of the studies asked how much the symptom burden distressed the patient (Table S10).

Sixteen studies provided data that related prevalence/severity of self-reported constipation with an HRQoL evaluation, clinical data, or laboratory test results (Table S11). Both the presence and severity of self-reported constipation were associated with a significantly worse HRQoL: both the physical and mental well-being of the CKD patients [35,39,53]. Analyses of symptom clusters led to different results: Lee SJ et al. found that constipation and diarrhea clustered together with the "difficulty sleeping" item into the "neurological and bowel problem" symptom cluster [35], whereas both Gutiérrez Sánchez et al. and Almutary et al. failed to cluster constipation together with other symptoms [31,69]. Interestingly, Dawson et al. found an association between taste disturbances and constipation prevalence [37], while the EQUAL study showed that constipation was an independent predictor of a decline in nutritional status [23]. Finally, Murtagh et al. showed that the prevalence of constipation within a month before death was 1.87 times higher than in the whole baseline CKD group [62,63]; nonetheless, the increase in the prevalence of constipation in CKD patients was evidenced also over the 1-year follow-up period in the EQUAL study [52].

Taken together, these data demonstrate that self-reported constipation is one of the most common lower GI symptoms and it is consistently associated with impaired HRQoL. In the case of patients with CKD G3/G4–5, more than half of constipated patients reported at least moderate severity of the symptom.

3.3.2. Functional Constipation

Data on the prevalence of functional constipation (FC) in CKD were reported in three studies [9,40,55]. Both individual and pooled data are shown in Figure 3.

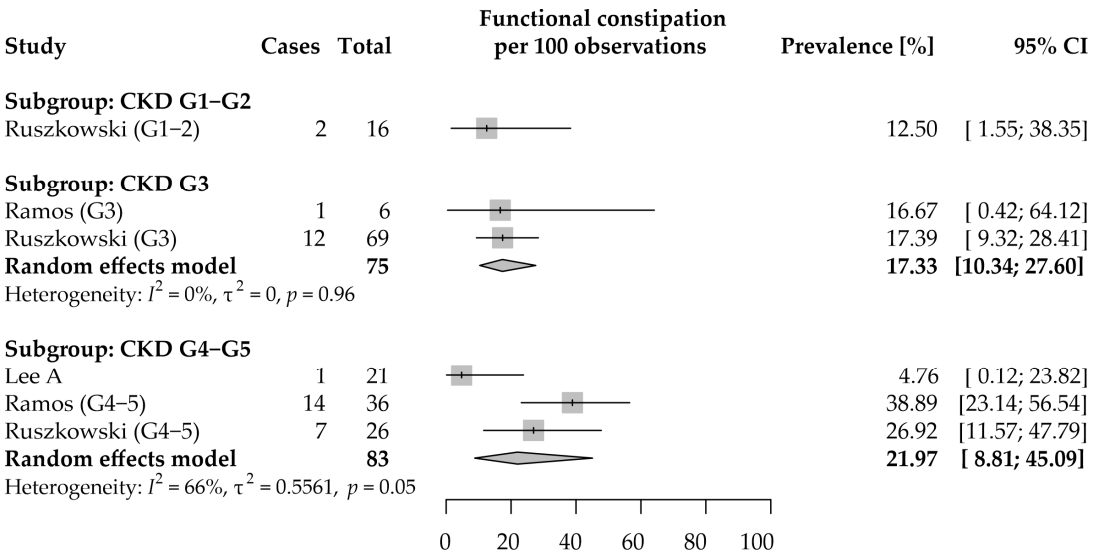

Figure 3. Forest plot with pooled point prevalence estimates for functional constipation in chronic kidney disease by stages.

Only one study reported the prevalence of FC among patients with CKD G1–2 (12.5%, 95% CI: 1.6–38.4% [9]); therefore, a meta-analysis was not performed for this subgroup.

A meta-analysis of FC prevalence in the CKD G3 subgroup was conducted using data from two studies [9,40]. The estimated average prevalence was 17.3% (95% CI: 10.3–27.6%). We did not detect significant between-study variance ($\tau^2 = 0$; $p = 0.96$; $I^2 = 0$).

A total of 3 studies were included in the analysis for the CKD G4–5 subgroup [9,40,55]. The estimated average prevalence of FC was 22.0% (95% CI: 8.8–45.1%). Data from the included studies were quite homogenous ($p = 0.05$), and it was estimated that two-thirds of the variability was due to between-study variance ($\tau^2 = 0.56$; $I^2 = 66\%$). There is high uncertainty about the prevalence of FC in future studies (95% PI ranged from 0 to 100%).

All extracted implications of FC were summarized in Table S12. Both Ramos et al. and Ruszkowski et al. failed to show significant associations between gender, age, or body mass index and the presence/prevalence of FC [9,40]. Additionally, Ramos et al. suggested no association between dietary parameters and FC [40], while Ruszkowski et al. showed that taking acetaminophen (paracetamol) was associated with higher, whereas non-steroidal anti-inflammatory drugs with lower, prevalence of FC [9]. Only one study explored (and found) relationships between the presence of FC and both HRQoL and sleep quality [9,46]. Ramos et al. failed to prove a statistically significant association between reporting FC and having higher levels of *p*-cresyl sulfate, one of the uremic toxins that are generated by gut microbiota [40].

In conclusion, even though available data on FC prevalence are quite homogenous, the estimation of the prevalence is uncertain due to data limitations. Further studies are needed to verify the described associations of FC with pharmacotherapy and HRQoL in the CKD population.

3.4. Diarrhea: Prevalence and Severity

Data on self-reported diarrhea prevalence in CKD were provided in 22 studies, of which 20 were included in the meta-analyses below (Figure 4). We did not identify any study reporting the prevalence of functional diarrhea in CKD. Studies reporting self-reported diarrhea were conducted primarily in the WHO Western Pacific (7 studies [24,35,37,42,58,64,67]) and European (6 studies [30,31,38,53,62,65]) Regions, whereas only one study each was conducted in the African (Nigeria [43]) and Eastern Mediterranean (Saudi Arabia [68]) Regions.

Data were collected using authors' questionnaires/during anamnesis in the case of 4 studies [30,42,43,66], and using validated questionnaires: the POS-S Renal questionnaire and its modifications/translations in 6 studies [24,27,31,35,64,65]; IPOS-Renal in 3 studies [37,39,67]; DSI in 3 studies [53,57,58]; MSAS-SF questionnaire in 2 studies [44,62]; CKD Symptom Index—Sri Lanka (CKDSI-Sri Lanka) in 2 studies [34,36]; and CKD Symptom Burden Index (CKD-SBI [68]) and Renal Disease Questionnaire (RDQ [38]) in one study each.

Three studies were included in the analysis for the CKD G1–2 subgroup [34–36]. The estimated average prevalence was 13.9% (95% CI: 6.4–27.3%). While the observed prevalence ranged from 0 to 27%, no significant heterogeneity was detected ($I^2 = 58\%$, $\tau^2 = 0.20$, $p = 0.09$). The prevalence in this subgroup in future studies is highly uncertain (95% PI: 0–99.8%). Two studies presented data that could be meta-analyzed for the symptom severity (Table S13). Mild, moderate, severe, and overwhelming severity of diarrhea was, on average, reported by 46.8% (95% CI: 15.5–80.9%), 20.0% (95% CI: 0–53.9%), 13.2% (95% CI: 0–40.2%), and 20.0% (95% CI: 0–53.9%) of CKD G1–2 patients reporting the symptom, respectively.

The CKD G3 subgroup analysis included 6 studies (663 patients) [34–39]. The estimated average prevalence was 13.7% (95% CI: 8.4–21.8%). The differences in the reported prevalence across studies (7–29%) resulted primarily from between-study variance ($\tau^2 = 0.35$; $I^2 = 86\%$). The 95% PI for the prevalence ranged from 2.5 to 49.5%. Five studies presented data that could be meta-analyzed for the symptom severity (Table S13). Among CKD G3 patients reporting the symptom, it was of mild, moderate, severe, and over-

whelming severity in the case of, on average, 63.0% (95% CI: 43.7–82.4%), 25.2% (95% CI: 9.8–45.4%), 8.0% (95% CI: 0–20.9%), and 3.8% (95% CI: 0–13.6%) of them, respectively.

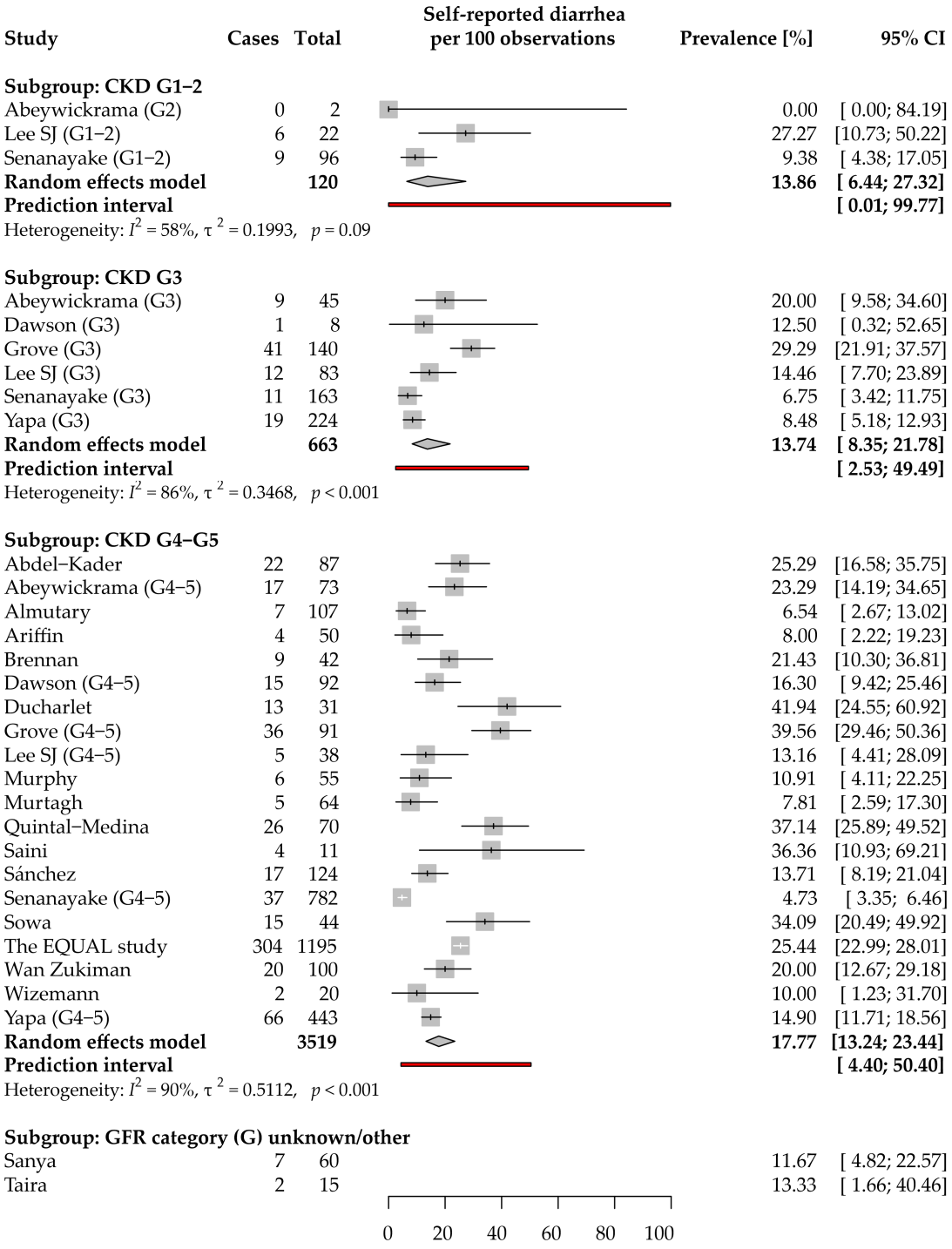

Figure 4. Forest plot with pooled point prevalence estimates for self-reported diarrhea in chronic kidney disease by stages.

The CKD G4–5 subgroup analysis included 20 studies (3519 patients) [23,24,26,27,30,31,34–39,42,44,53,57,58,62,64,65,68]. The estimated average prevalence was 17.8% (95% CI: 13.2–23.4%). The reported prevalence ranged from 5 to 42% and resulted mainly from the between-study variance (τ^2 = 0.51; I^2 = 90%). A subgroup analysis revealed that it may have partially resulted from the difference in the location of data collection (p < 0.001); studies

conducted in the American and Western Pacific Regions reported higher prevalence than studies from the South-East Asian or Eastern Mediterranean WHO Regions (Table S14). Neither study period, average age of participants, nor sex of participants were significantly associated with the reported prevalence. While there was no asymmetry in the funnel plot (Peters' regression test: $p = 0.54$), an analysis of both the Doi plot and the LFK index suggested a major bias favoring the publication of studies with a lower prevalence of self-reported diarrhea in CKD G4–5 (Figure S4). The 95% PI for the prevalence in new studies ranged from 4.4 to 50.4%. Based on studies that simultaneously reported the prevalence in several CKD stages, no significant differences in the odds of reporting the symptoms were found between CKD G3 patients and either G1–2 ($p = 0.16$) or G4–5 ($p = 0.23$) (Figures S5 and S6). We included 10 studies in the meta-analysis of diarrhea severity in CKD G4–5 (Table S13). Mild, moderate, severe, and overwhelming severity of diarrhea was, on average, reported by 47.1% (95% CI: 33.3–59.7%), 35.6% (95% CI: 23.0–48.2%), 13.5% (95% CI: 5.4–23.6%), and 3.9% (95% CI: 0.1–10.9%) of CKD G4–5 patients reporting the symptom, respectively.

All extracted relationships between self-reported diarrhea and HRQoL, clinical data, or laboratory test results are presented in Table S15. Interestingly, in contrast to the clear picture of the relationship between HRQoL and constipation, there are controversies on this in the case of diarrhea. The EQUAL study did show negative implications of self-reported diarrhea on both the physical and mental components of HRQoL (in a similar way as in the case of constipation) [53]. Contrary to this, Yapa et al. found no significant correlation between diarrhea severity and either the physical or mental components of HRQoL [39].

Analyses of symptom clusters led, however, to quite consistent results. According to Almutary et al. nausea and vomiting were core symptoms of the GI symptom cluster across all dimensions; diarrhea was related to this cluster in distress and severity dimensions only [69]. Similarly, Gutiérrez Sánchez et al. reported that diarrhea was clustered together with nausea and vomiting [60]. On the other hand, Lee SJ et al. found that diarrhea and constipation clustered together with the "difficulty sleeping" item into the "neurological and bowel problem" symptom cluster [35].

The pathophysiology of self-reported diarrhea in CKD remains unclear. Two research teams from Nigeria failed to show an association between diarrhea and cardiovascular autonomic neuropathy (autonomic dysfunction) in CKD [43,54]; however, nocturnal diarrhea might be a predictor of this dysfunction [54]. Gordon et al. suggested bile acid abnormalities as a cause of diarrhea in CKD [41], but definitely more studies are needed to confirm this hypothesis.

To sum up, the above-mentioned data indicate that self-reported diarrhea is less common than self-reported constipation in non-dialyzed CKD patients. Unfortunately, no study used Rome criteria, and thus functional diarrhea prevalence remains unknown in CKD. The sophisticated analyses of numerous symptoms suggested that self-reported diarrhea can be somehow related to both nausea and vomiting; however, the understanding of self-reported diarrhea pathobiology in CKD is extremely limited.

3.5. Bloating: Prevalence and Severity

Data on the self-reported bloating prevalence in CKD were extracted from 9 studies [9,12,30,32,42,44,47,56,62] that enrolled 4128 participants (Figure 5). All but one study were included in the meta-analyses. Four studies each were from the WHO European [9,30,44,62] and Western Pacific [12,42,47,56] Regions; one study reported data acquired in the Region of the Americas [32]. The included studies were characterized by using different methods to collect data on symptom prevalence: three used face-to-face interview/authors' questionnaires; two, the MSAS-SF questionnaire [44,62]; each of the other studies used a different questionnaire.

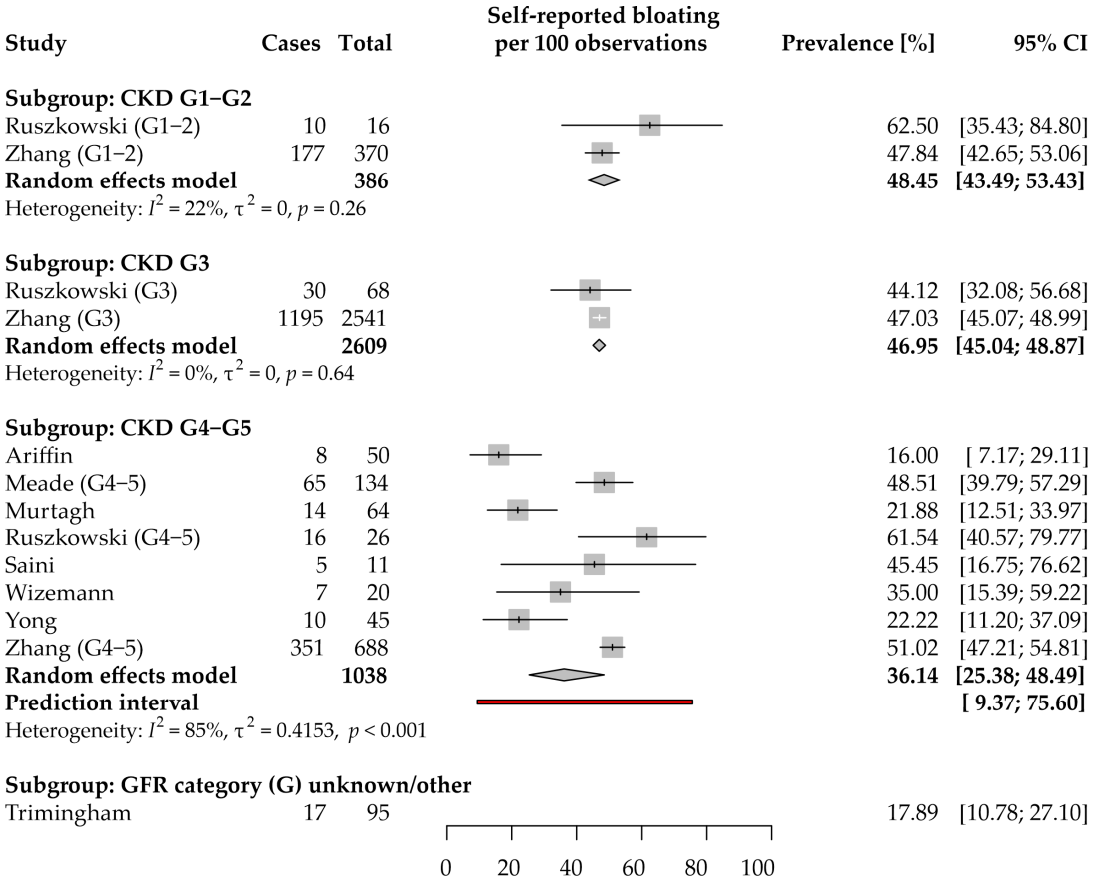

Figure 5. Forest plot with pooled point prevalence estimates for self-reported bloating in chronic kidney disease by stages.

Based on two studies [9,32], the estimated average prevalence in the CKD G1–2 subgroup was 48.45% (95% CI: 43.5–53.4%). There was no significant heterogeneity between the data from both studies ($\tau^2 = 0$; $I^2 = 22\%$; $p = 0.26$).

The same two studies were the only source of data for the CKD G3 subgroup. The estimated average prevalence was 46.95% (95% CI: 45.0–48.9%). Data from both studies were consistent ($\tau^2 = 0$; $I^2 = 0\%$; $p = 0.64$).

The CKD G4–5 subgroup analysis included 8 studies [9,30,32,42,44,47,56,62]. The estimated average prevalence was 36.1% (95% CI: 25.4–48.5%). The results of the included studies ranged between 16 and 62%, and the differences can be attributed mainly to the between-study variance ($\tau^2 = 0.42$; $I^2 = 85\%$). The 95% PI for the prevalence in new studies ranged from 9.4 to 75.6%. Based on two studies that simultaneously reported the prevalence in all CKD stages, no significant differences in the odds of reporting the symptoms were found between CKD G3 patients and either G1–2 ($p = 0.55$) or G4–5 ($p = 0.21$) (Figures S7 and S8).

Table S16 summarizes the data on the severity of abdominal bloating. Only one study reported data for the CKD G1–2 and G3 subgroups [9]. Among 10 CKD G1–2 patients with the symptom, 80.0% (95% CI: 70–100%) experienced mild, and 20.0% (95% CI: 10.0–48.7%) moderate severity of bloating, while severe or overwhelming bloating was reported by 0% (95% CI: 0–34.3%) of patients each. Among 30 CKD G3 patients with abdominal bloating, mild severity was reported by 50.0% (95% CI: 33.3–68.2%), moderate by 46.7% (95% CI: 30.0–64.8%), severe by 3.3% (95% CI: 0–21.5%), and overwhelming by 0% (95% CI: 0–18.2%). Three studies provided results on bloating severity in CKD G4–5, but data could have not been meta-analyzed (Table S16).

Table S17 summarizes the implications of abdominal bloating in CKD patients. Each of the findings was reported in a single study; therefore, the generalizability of the bloating implications may be limited.

Taken together, even though self-reported bloating seems to be one of the most common GI symptoms, its prevalence in the early stages of CKD has rarely been studied. Moreover, no study provided data on the risk factors associated with the increased burden of the symptom in CKD. Since no study used Rome criteria, functional bloating prevalence remains unknown in CKD.

3.6. Abdominal Pain: Prevalence and Severity

Only four studies provided data on the self-reported abdominal pain prevalence in CKD (Figure 6) [9,12,30,42]. Two studies each were from the WHO European [9,30] and Western Pacific [12,42] Regions. The included studies were characterized by using different methods to collect data on symptom prevalence: two used face-to-face interviews, the others used questionnaires such as the Patient Assessment of Constipation-Symptoms (PAC-SYM) questionnaire, and the "Bowel health questionnaire". Additionally, one study each presented results on autosomal dominant polycystic kidney disease (ADPKD) [49] and CKD secondary to Fabry disease [25]. We did not identify any study providing data about the prevalence of centrally mediated abdominal pain syndrome in CKD. The prevalence of abdominal pain in CKD secondary to ADPKD or Fabry disease is described in Supplementary Materials, Results S2.

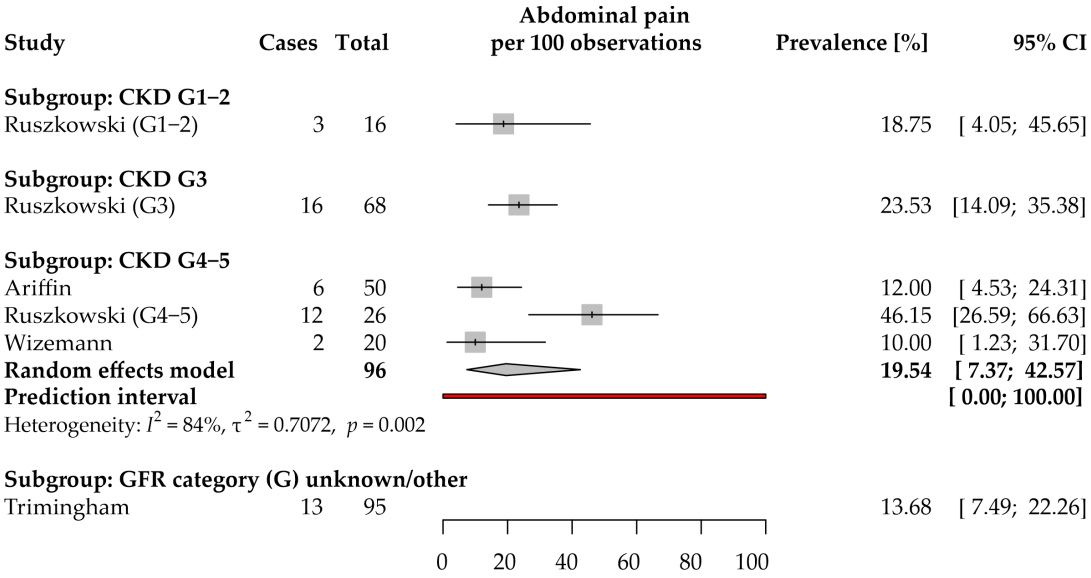

Figure 6. Forest plot with pooled point prevalence estimates for self-reported abdominal pain in chronic kidney disease by stages.

Data on self-reported abdominal pain prevalence among patients with CKD G1–2 (18.8%; 95% CI: 4.1–46.7%) and CKD G3 (23.5%; 95% CI: 14.1–35.4%) were extracted from only one study [9]; therefore, meta-analyses were not performed for these subgroups.

The CKD G4–5 subgroup analysis included 3 studies [9,30,42]. The estimated average prevalence was 19.5% (95% CI: 7.4–42.6%). Ruszkowski et al. [9] observed substantially higher prevalence than in the other two studies; the difference was unlikely from sampling variance (τ^2 = 0.71; I^2 = 84%). We suppose this is due to the use of paper questionnaires by Ruszkowski et al. and face-to-face interviews by the other two research teams. The prevalence in future studies is totally uncertain (95% PI: 0–100%).

Three studies provided data on the symptom implications (Table S19). Briefly, Ruszkowski et al. analyzed the associations between abdominal pain and both HRQoL and quality of sleep

in CKD [9,46]. Miskulin et al. questioned the association between either eGFR or height-adjusted total kidney volume and abdominal pain in ADPKD patients [49].

In conclusion, based on both the limited number and heterogeneous characteristics of the included studies, the results are uncertain. Additionally, there were no data on the symptom prevalence coming from the CKD populations living in the African, American, South-East Asian, and Eastern Mediterranean Regions.

3.7. Stool Consistency (Bristol Stool Scale)

The stool appearance and consistency were classified with the Bristol Stool Form Scale (BSFS) into seven stool types. Types 1–2 represent abnormally hard stools (and in conjunction with other symptoms indicative of FC or the constipation-predominant subtype of irritable bowel syndrome), while types 6–7 represent abnormally liquid stools.

Six studies provided data on stool consistency in CKD patients: five studies reported prevalence of both types 1–2 and 6–7 stool forms among 482 patients [9,12,33,40,47], while one study provided data on types 1–2 only in 21 patients [55]. All studies were conducted or published after 2015, and came from Australia (3 studies: [12,47,55]), Europe (2 studies: [9,33]), and Brazil [40]. Table 2 shows the extracted and pooled prevalence of stool types 1–2, 3–5, and 6–7.

Two studies, both conducted in Europe, were included in the prevalence analysis for the CKD G1–2 subgroup [9,33]. The estimated average prevalence of types 1–2 was 14.8% (95% CI: 0.8–37.5%), whereas for types 6–7, it was 8.0% (95% CI: 0–24.2%). While the prevalence of types 3–5 was similar in both studies (76–77%), the prevalence of having either abnormally hard, or loose, stool was quite different in these studies (I^2 = 61%).

Three studies were included in the prevalence analysis for the CKD G3 subgroup [9,33,40]. The estimated average prevalence of types 1–2 was 23.0% (95% CI: 10.9–37.3%), whereas for types 6–7, it was 13.2% (95% CI: 4.1–25.5%). Nearly a half of the total variance can be attributed to sampling errors (I^2 = 54%).

Four studies were included in the prevalence analysis for the CKD G4–5 subgroup [9,33,40,47]. The estimated average prevalence of types 1–2 was 24.5% (95% CI: 13.2–37.8%), whereas for types 6–7, it was 15.7% (95% CI: 6.5–27.6%). There was substantial between-studies heterogeneity (τ = 0.058, I^2 = 72%); however, the elimination of results from [47] would reduce the estimated I^2 to 0% and lead to higher estimates for the prevalence of both hard stools (30.8%) and loose stools (17.0%).

The relationships between stool consistency and other data are shown in Table S20. Briefly, two research teams found that the harder the stool consistency, the higher the concentration of some uremic solutes such as *p*-cresyl sulfate and hippuric acid in serum/plasma [33,40,48]. Both Meade et al. and Ramos et al. reported no associations between dietary parameters and stool consistency [40,47]. Ruszkowski et al. found that taking diuretics was independently associated with an increased prevalence of reporting type 1–2 (i.e., hard) stool form [9]. Interestingly, implications for HRQoL were explored in one study only: no associations between types 1–2 form and either HRQoL or sleep quality were found [9,46].

To sum up, the results of a small number of studies suggest that about two-fifths of patients with advanced CKD may have abnormal stool consistency. Unlike self-reported constipation and diarrhea, stool form appears to be less related to lower HRQoL and more related to increased concentrations of uremic toxins, or at least those formed in the lumen of the large intestine. Further studies, especially outside of Europe and Australia, are needed to assess the impact of CKD progression and frequently used drugs on stool consistency (e.g., via alternation of whole gut transit time). With the help of multi-omics data, it will be possible to identify more uremic solutes associated with hard stool consistency.

Table 2. Stool consistency in chronic kidney disease according to Bristol Stool Form Scale.

Authors, Reference	Total (N Analyzed)	Bristol Stool Form Scale		
		Type 1–2	Type 3–5	Type 6–7
CKD G1–2				
Gryp, T.; et al. [33]	37	4	28	5
Ruszkowski, J.; et al. [9,46]	13	3	10	0
Prevalence (95% CI) [a]		14.8% (0.8–37.5)	77.2% (51.8–94.9)	8.0% (0–24.2)
CKD G3				
Gryp, T.; et al. [33]	44	7	27	10
Ramos, C.I.; et al. [40]	6	1	5	0
Ruszkowski, J.; et al. [9,46]	62	19	37	6
Prevalence (95% CI) [b]		23.0% (10.9–37.3)	63.8% (47.5–77.6)	13.2% (4.1–25.5)
CKD G4–5				
Gryp, T.; et al. [33]	33	9	18	6
Meade, A.; et al. [47]	134	18	98	18
Ramos, C.I.; et al. [40]	36	13	18	5
Ruszkowski, J.; et al. [9,46]	22	6	12	4
Lee, A.; et al. [55]	21	4	17	
Prevalence (95% CI) [c]		24.5% (13.2–37.8)	59.8% (45.3–73.2)	15.7% (6.5–27.6)
CKD: eGFR unknown				
Trimingham, C.; et al. [12]	95	9	77	9
Prevalence (95% CI) [d]		9.5% (3.2–17.6)	81.1% (74.7–89.1)	9.5% (3.2–17.6)

[a] Meta-analysis was conducted using a random-effects model with Freeman–Tukey double arcsine transformation of proportions ($\tau^2 = 0.079$; $I^2 = 61\%$). [b] Meta-analysis was conducted using a random-effects model with Freeman–Tukey double arcsine transformation of proportions ($\tau^2 = 0.038$; $I^2 = 54\%$). [c] Meta-analysis of 4 studies was conducted using a random-effects model with Freeman–Tukey double arcsine transformation of proportions ($\tau^2 = 0.058$; $I^2 = 72\%$); data provided by Lee A were not included due to an incompatible format. [d] Confidence intervals for multinomial proportions were calculated according to the method of Sison and Glaz.

3.8. Number of Bowel Movements per Week

Data on the number of bowel movements per week were extracted from three studies [9,12,47] enrolling 339 CKD patients, and one study [45] enrolling 2245 DKD patients. Three studies were conducted in the Western Pacific Region (Australia [12,47] and Japan [45]), and one in Europe (Poland [9]). The authors used their own questionnaires to collect data on the outcome.

Data on the weekly frequency of defecation among patients with CKD G1–2 and CKD G3 were extracted from one study only [9]; therefore, meta-analyses were not performed for these subgroups. Estimated prevalence and its 95% CI based on this study for both subgroups are presented in Table S21. We were able to conduct a meta-analysis for the CKD G4–5 subgroup with data from two studies [9,47]: commonly, CKD G4–5 patients had a BM once daily [40.5% (95% CI: 9.4–72.4%)], whereas 31.9% (95% CI: 4.4–64.4%), 26.1% (95% CI: 1.8–58.5%), and 1.5% (95% CI: 0–14.7%) CKD G4–5 patients had more than 7, less than 7 but at least 3, and less than 3 BMs per week, respectively (Table S21).

The identified relationships between the number of BMs per week and HRQoL, clinical data, or laboratory test results are presented in Table S22. Interestingly, the frequency lower than 7 BMs/week (i.e., less than once a day) was associated with impaired HRQoL in CKD,

and an increased risk of nephropathy in patients with diabetes. However, since each of the implications was reported in a single study, the generalizability of the implications is limited.

To conclude, the described implications of having a bowel movement less than once a day seem worthy of more extensive research, especially since information on BM frequency is easy to obtain.

3.9. Fecal Incontinence and Rectal Pain

Two outcomes, the prevalence of both fecal incontinence and rectal pain in non-dialysis CKD patients, were reported in one study only [47]. It came from Australia, and the symptoms were assessed using a modified 28-item Gastrointestinal Symptom Rating Scale. Fecal incontinence was reported by 46 [34.3% (95% CI: 26.4–43.0%)] and rectal pain by 18 [13.4% (95% CI: 8.2–20.4%)] out of 134 CKD G4–5 patients. The prevalence of both symptoms in earlier CKD stages, as well as in another geographical localization, remain unknown.

The authors of the mentioned study stated that in the combined group of non-dialysis and dialysis CKD patients, "there was no significant association of fruit, vegetables, whole-grains or legumes intake with any GI symptom" (p not reported) [47].

In light of the sparse data presented above, patients with CKD G4–5 may have a surprisingly high prevalence of fecal incontinence; however, without further research the actual prevalence, especially outside Australia, remains unknown.

3.10. Sensitivity Analyses

The estimated pooled prevalence of the symptoms remained stable in sensitivity analyses, and the differences between the reference and other models were, in more than four-fifths of the cases, lower than 1%. We listed all estimates with a difference greater than one percent in Table S23.

4. Discussion

Our study aimed to comprehensively determine the prevalence, severity, and implications of lower GI symptoms in non-dialysis CKD patients. This population required special interest because non-dialyzed patients constitute more than 99% of all CKD patients, whereas, when compared to other frequent conditions, the overall burden of CKD is very high [1]. By focusing on a single symptom group, and using a widespread search strategy (including citation chasing of symptoms questionnaires), we uncovered a significant number of papers previously overlooked in the context of assessing CKD symptom prevalence. Lower GI symptoms, particularly abdominal bloating and self-reported constipation, are common in non-dialysis CKD patients, but their severity is limited. The literature showed the multiple relationships between lower GI symptoms and HRQoL, clinical outcomes, and laboratory data [9,23,35,39,40,46,49–53]. Our work is the first to analyze in detail the knowledge of lower GI symptomatology in non-dialysis-dependent CKD; thus, most likely for the first time, we demonstrated some novel findings that could not be concluded with sufficient certainty from the original studies (e.g., increased odds of self-reported constipation in CKD patients with more advanced disease). The meta-analysis of results from multiple studies makes the conclusions more convincing and verifies previous smaller observations with higher statistical power.

In an excellent narrative review by Sumida et al. fully dedicated to constipation in CKD [5], the part about constipation epidemiology was based mainly on the information about symptom prevalence in dialysis patients (systematically reviewed earlier [10]). Sumida et al. highlighted a scarcity of information on the prevalence of constipation among non-dialysis-dependent CKD patients. We believe that our work, with several meta-analyses on such specific outcomes as the prevalence of self-reported constipation, FC, or hard stool consistency, at least partially fills the knowledge gap identified by Sumida et al. and provides details on lower GI symptoms experienced in CKD. Our findings can be used

to update the Kidney Disease: Improving Global Outcomes (KDIGO) report on Supportive Care in CKD [70]. In this report, the prevalence of "constipation" and "diarrhea" was based on 17 and 10 studies, respectively. Not only did we include more studies and specify the meaning of the symptoms, but we also properly analyzed the outcomes in subgroups according to the deterioration of kidney function. More importantly, the report's authors stated that the "Impact (of either constipation or diarrhea on HRQoL, morbidity, etc.) has not been assessed systematically in CKD". Our work covers the knowledge gap and illuminates the importance of lower GI symptoms in patients' experience of CKD.

Since the included studies rarely tested whether the prevalence of GI symptoms differed between CKD patients and the general population [42,66], only a less certain indirect comparison can be made using published data on the prevalence of the symptoms in the general population. It seems that, in comparison to the general population, self-reported abdominal bloating and both functional and self-reported constipation are more common in CKD non-dialysis patients (details in Appendix A). Interestingly, non-dialysis patients have similar odds of reporting abdominal bloating and constipation but might have lower odds of reporting diarrhea when compared with dialysis patients (details in Appendix B).

4.1. Limitations of the Evidence Included and the Review Processes Used

Below, we discuss limitations of the included evidence, such as a lack of studies reporting several outcomes, a scarcity of studies from some world regions, and the risk of bias in the included studies.

We did not identify any study providing data about the prevalence of functional diarrhea, functional abdominal bloating/distension, centrally mediated abdominal pain syndrome, or functional anorectal pain in CKD. Given the fact that all functional GI disorders are associated with lower HRQoL in the general population [8], covering this knowledge gap is relevant.

The meta-analysis methodology provides the possibility to estimate average prevalence across studies. We cannot, however, make informed statements about the prevalence among populations that were not covered by primary studies. That is, the paucity of studies from the African and the Eastern Mediterranean Regions means that knowledge of symptom prevalence among CKD patients living there is limited. Moreover, the extrapolation of the available results to unexamined populations (by continent or ethnicity) may lead to improper conclusions, as significant variations between populations have been described in such aspects as normal bowel movement frequency, and both the prevalence, and core symptoms, of functional GI disorders [8,71–73].

Furthermore, the design of the majority of the included studies could introduce a risk of bias. Participants were recruited using convenience sampling rather than recommended methods such as random sampling or inclusion of all patients from a census. It may have led to the selection of nonrepresentative groups of CKD patients (e.g., wanting to express their GI problems in surveys). Such a risk of bias could have been exacerbated further because of the too-narrow inclusion/too-wide exclusion criteria used in a part of the included studies.

Finally, we extracted "implications" in a similar way as in the KDIGO Report on Supportive Care in CKD [70]. That is, we collected data on all reported associations between GI symptoms and HRQoL/clinical data/laboratory test data. Unfortunately, the vast majority of the included studies had a cross-sectional design and did not apply more or less sophisticated methods of causal inference; therefore, the reported associations should not be treated as causal relationships.

We put in a lot of effort to use the most up-to-date and most appropriate methods to meta-analyze the collected data. Nonetheless, we found some limitations in the available methods. Firstly, there are no well-established one-step methods to meta-analyze multinomial data such as symptom severity, stool consistency, and frequency of BMs. We employed a commonly-used multi-stage technique that is implemented in MetaXL and is

based on the Freeman–Tukey double arcsine transformation of proportions to stabilize their variances [22]. Even though MetaXL uses the DerSimonian and Laird method to estimate between-study variance, there is a paucity of simulation research that would confirm that it is the optimal approach (it was, however, shown to be a suboptimal method in other conditions [74]). Another alternative that recently emerged is a Bayesian approach that works under the assumption that each category prevalence understood as the probability is distributed as a Dirichlet distribution with a gamma hyperprior [75]. We also found that there is a lack of a validated method to plot a multinomial data meta-analysis. Therefore, we will plan to design several visualizations and test their readability in both experienced and not-experienced users of systematic reviews. In this review, we provided tabulated data, and showed the results in plain text. Because the number of studies included in our meta-analyses was limited, the estimations of both the between-study variance (τ) and I^2 statistic could be imprecise or even biased [76]. We believe that our work will encourage the next research teams to examine the prevalence and severity of GI symptoms in CKD patients, and that we will be able to include many more studies in the update of our work in the next 3–4 years. With new studies, all estimations will be more precise.

4.2. Implications of the Results for Practice and Future Research

Below, we discuss how our findings may be applied directly to improve the quality of patient care and to enhance the design and objectives of future research.

Numerous questionnaires designed to assess symptoms in CKD patients do not include questions about the lower GI symptoms (e.g., Symptoms and Problems Subscale from the Kidney Disease Quality of Life 36-item Short Form Survey (KDQOL-36™)). Since patients with GI symptoms may incorrectly evaluate their GI health and rarely discuss their symptoms with a clinician, it is of great importance to actively ask patients about GI symptoms [11,12,77]. Therefore, in agreement with van der Willik et al. [78], we recommend the DSI and the POS-S Renal (and its expanded version: the IPOS-Renal) for routine symptom assessment in CKD patients. Additionally, specific GI questionnaires may be useful for research purposes. Given the especially high prevalence of abdominal bloating and self-reported constipation in CKD, future studies should more frequently use such questionnaires as the Intestinal Gas Questionnaire [79,80] and the PAC-SYM [81] questionnaire. In addition, because of the paucity of data, there is a need to assess the prevalence, risk factors, and implications of functional disorders in CKD; the optimal way is to use the Rome IV Diagnostic Questionnaire for Functional Gastrointestinal Disorders in Adults. The use of specialized questionnaires will improve understanding of patients' GI symptoms and, when combined with multi-omics data, may reveal the role of GI symptoms in the gut–kidney axis in CKD [82].

According to the evidence-based research approach, not only did we provide pooled prevalence estimates, but we also identified many evidence gaps. Our study may, therefore, serve to calculate sample sizes and choose relevant outcomes in future studies [83]. Furthermore, to gain greater insight into the associations found in cross-sectional studies (e.g., self-reported constipation with HRQoL), there is a need for more high-quality longitudinal studies that will apply causal inference methods [84]. As the pathophysiology of GI symptoms in CKD remains poorly understood, we suggest a wide exploration of both traditional risk factors (including gender, physical activity, and fiber intake [85]) and CKD-related disorders/processes that can contribute to symptoms (e.g., dysregulation of the autonomic nervous system, endocrine disorders, bile acids composition abnormalities, or specific drug side-effects). Finally, the treatment burden inherently associated with CKD (e.g., difficulties associated with taking medicine, problems resulting from fluid restriction, psychological barriers to accessing public toilets in hospital) should be taken into account [86].

The high prevalence of lower GI symptoms should be taken into account in studies focusing on the alteration of GI microbiota in CKD patients. Previous studies have linked several lower GI symptoms with dysbiosis in the general population [87,88], so how it is related to the dysbiosis observed in CKD must be revealed [89]. Surprisingly, none of the

studies to date have included patient GI symptomatology in the assessment of dysbiosis in CKD, with one exception that found that variation of the microbial composition was correlated with stool consistency [48].

Finally, interventional studies should be conducted to assess whether symptomatic treatment enhances HRQoL in the case of GI symptoms that were shown to be associated with a worse HRQoL.

As the pace of research on CKD symptomatology increases, we plan to update this systematic review in approximately 3–4 years. This will include broader search methods to include areas not fully covered in this review and will take advantage of emerging methods for meta-analyses. We anticipate the results of a study currently occurring in Uganda [90], and also one in Australia [91], and a full-text article detailing data for non-dialysis CKD patients from a study conducted in Malaysia [92]. Moreover, we will update the meta-analytical methods to provide results that are as reliable as possible.

5. Conclusions

The collected data demonstrated that lower GI symptoms, especially abdominal bloating and self-reported constipation, are common in non-dialysis CKD patients, but the severity of the majority of GI symptoms is limited. The lower GI symptoms in CKD warrant interest not only due to their associations with lower HRQoL, but also because of their probable implications indicated in individual reports. Our findings can be used in clinical practice to improve the recognition of GI symptoms in CKD (medical practitioners should use symptom questionnaires that incorporate the most prevalent GI symptoms), as well as in future research to explore knowledge gaps that were identified. To elucidate the pathogenesis of lower GI symptoms in CKD, longitudinal studies using specialized questionnaires and collecting multi-omics data are needed. Because of the variability in GI symptoms' prevalence worldwide, more data have to be collected, especially in the African and Eastern Mediterranean Regions. All meta-analysis results can be incorporated into the sample size estimation of future studies. Given the widespread GI symptoms in CKD, they should be taken into account in studies evaluating the GI microbiome in CKD.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm11216363/s1, Figure S1: Funnel and Doi plot for self-reported constipation in CKD G4–5; Figure S2: Forest plot with pooled odds ratio for self-reported constipation in chronic kidney disease (G4–5 vs. G3); Figure S3: Bubble plot based on meta-regression model: odds ratio for self-reported constipation in chronic kidney disease (G4–5 vs. G3); Figure S4: Funnel and Doi plot for self-reported diarrhea in CKD G4–5; Figure S5: Forest plot with pooled odds ratio for self-reported diarrhea in chronic kidney disease (G3 vs. G1–2); Figure S6: Forest plot with pooled odds ratio for self-reported diarrhea in chronic kidney disease (G4–5 vs. G3); Figure S7: Forest plot with pooled odds ratio for self-reported abdominal bloating in chronic kidney disease (G3 vs. G1–2); Figure S8: Forest plot with pooled odds ratio for self-reported abdominal bloating in chronic kidney disease (G4–5 vs. G3); Table S1: Deviations from the registered protocol with justification; Table S2: Search strategy; Table S3: Symptom questionnaires used for forward citation chasing; Table S4: Items of electronic extraction form; Table S5: Excluded studies with reason; Table S6: Exclusion criteria in the included studies; Table S7: Risk of bias in included studies; Table S8: Severity of self-reported constipation; Table S9: Subgroup analysis for self-reported constipation prevalence in chronic kidney disease (CKD) G4–5; Table S10: Severity of self-reported constipation (alternative version); Table S11: Relationships between self-reported constipation and health-related quality of life (HRQoL), clinical data, or laboratory tests results; Table S12: Relationships between functional constipation and HRQoL, clinical data, or laboratory tests results; Table S13: Severity of self-reported diarrhea; Table S14: Subgroup analysis for self-reported diarrhea prevalence in CKD G4–5; Table S15: Relationships between self-reported diarrhea and HRQoL, clinical data, or laboratory test results; Table S16: Severity of abdominal bloating; Table S17: Relationships between self-reported abdominal bloating and HRQoL, clinical data, or laboratory test results; Table S18: Abdominal pain prevalence and severity in autosomal dominant polycystic kidney disease; Table S19: Relationships between self-reported abdominal pain and HRQoL, clinical data, or laboratory tests

results; Table S20: Relationships between stool consistency and HRQoL, clinical data, or laboratory tests results; Table S21: Number of bowel movements per week in patients with CKD or diabetic kidney disease; Table S22: Relationships between the frequency of defecations and HRQoL, clinical data, or laboratory tests results; Table S23: Sensitivity analysis: differences from the reference model exceeding one percent; Supplementary Methods, S1: Eligibility Criteria, S2: Reporting bias assessment, S3: Confidence interval calculation, subgroup analysis, sensitivity analysis, and certainty assessment; Supplementary Results, S1: Study characteristics, S2: Abdominal pain in ADPKD and Fabry disease. References [9,12,18,20,23–69,93–103] are mentioned in Supplementary Methods.

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Appendix A

Only two studies directly compared the prevalence of GI symptoms between CKD patients and the general population [42,66]. The analyses were, however, underpowered to find significant differences between groups (with one exception: Taira et al. found a higher prevalence of constipation among 15 CKD patients than in 76 healthy individuals [13% vs. 1%, $p = 0.02$]) [66].

Our study showed that the prevalence of self-reported constipation in CKD was 31.8% (95% CI: 13.9–54.9%), 29.8% (95% CI: 21.2–40.1%), and 38.8% (95% CI: 30.9–47.4%), in G1–2, G3, and G4–5 CKD stages, respectively. The median prevalence of self-reported constipation in the general population across 22 studies identified in five systematic reviews was 15.1% (IQR: 6.3–24.3%) [104–109]. Therefore, in comparison to the general population, self-reported constipation prevalence may be higher in CKD patients even in the early stages of the disease (similar in G1–2 and G3), and further increase with the loss of kidney function (G4–5). In a systematic review and meta-analysis conducted by Barberio et al. the prevalence of functional constipation (according to Rome III criteria, which were used in all studies included in our review) in the general population was 10.4% (95% CI: 6.5–14.9%; $I^2 = 99.8\%$) [98]. Therefore, in comparison to the general population, the FC prevalence is comparable in patients with early stages of CKD (G1–2: 12% [1.6–38.4%]), but may be increased in patients with CKD G3 (17.3% [10.3–27.6%]), and the difference may be bigger in stages G4–5 (22.0% [8.8–45.1%]).

Self-reported abdominal bloating is reported to be one of the most prevalent GI symptoms in the general population; it was also the most prevalent symptom in our analysis. We found that its point prevalence in CKD was 48.45% (95% CI: 43.5–53.4%; 2 studies), 46.95% (95% CI: 45.0–48.9%; 2 studies), and 36.1% (95% CI: 25.4–48.5%; 8 studies), in G1–2, G3, and G4–5 stages, respectively. Unfortunately, the prevalence of self-reported bloating

in the general population was not a focus of any systematic review up to date. The median prevalence of self-reported abdominal bloating in the general population across 9 studies was 20.6% (IQR: 13.4–31.4%). Therefore, in comparison to the general population, self-reported abdominal bloating prevalence seems to be higher in CKD patients, particularly in the early stages of the disease (similar in G1–2 and G3).

Appendix B

As stated in Table S10, nine studies directly compared the prevalence of self-reported constipation between non-dialysis patients with advanced stages of CKD and dialysis-dependent patients; the results were highly inconsistent. There were studies showing both lower (significantly: [31]; non-significantly: [39,55–58]) and higher (significantly: [68]; non-significantly: [24,42]) odds of self-reported constipation in dialysis patients than in patients with CKD G4–5. The median prevalence of self-reported constipation in dialysis patients across 13 studies identified in the systematic reviews conducted by Zuvela et al. [10] and our work was 30.1% (IQR: 25.7–43.2%), which is quite similar to the prevalence in CKD (particularly, the early stages). To sum up, there is no evidence supporting the hypothesis that dialysis patients have a significantly different prevalence of self-reported constipation than non-dialysis patients with CKD G4–5.

In the case of self-reported diarrhea (Table S14), there were eight studies that directly compared its prevalence between CKD non-dialysis and dialysis-dependent patients. In the majority of studies, non-dialysis patients had lower odds of reporting diarrhea (significantly in four studies: [24,36,39,68]; non-significantly in three studies: [31,42,57]) than patients treated with dialysis; only one study showed another trend [58]. The median prevalence of self-reported diarrhea in dialysis patients across 12 studies identified in the systematic reviews conducted by Zuvela et al. and our work was 16.9% (IQR 9.7–28.4) [10]; that is close to the average prevalence in G4–5 in our meta-analysis. To sum up, non-dialysis patients with advanced stages of CKD may have a lower or comparable prevalence of self-reported diarrhea than patients requiring dialysis.

As stated in Table S16, only two studies directly compared the prevalence of self-reported bloating between CKD non-dialysis and dialysis-dependent patients: both observed a slightly higher prevalence in dialysis patients but found no significant differences between these two groups [42,56]. The median prevalence of self-reported bloating in dialysis patients across 5 studies identified in the systematic reviews conducted by Zuvela et al. and our work was 27.6% (IQR 21.5–41.7%) [10], which is within the confidence interval of the average prevalence in CKD G4–5. Taken together, there are not enough data to reliably compare abdominal bloating prevalence between non-dialysis patients with advanced stages of CKD and dialysis-dependent CKD patients.

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Supplementary Material to:

Prevalence and Severity of Lower Gastrointestinal Symptoms amongst Non-Dialysis Chronic Kidney Disease Patients: A Systematic Review and Meta-Analysis

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Supplementary Contents

Supplementary Methods

S1. Eligibility Criteria

Population and settings

Inclusion: Adults (age ≥ 18 years) with CKD that are treated without dialysis.

Exclusion: People under 18 years of age; pregnant women; treatment with dialysis; inpatients (being at an inpatient facility for more than one day)

Since we were interested in the symptomatic profile of the CKD population in community-based settings, only outpatients receiving non-acute care or non-receiving any treatment were included. We restricted the scope of our interest to the patients not receiving dialysis therapy because renal replacement therapies are linked with several additional factors that may contribute to symptomatology. Studies in any geographic location were included.

Outcome

Primary outcomes were self-reported symptoms as follows: 1-2. Prevalence and severity of abdominal pain. 3-4. Prevalence and severity of abdominal bloating. 5-6. Prevalence and severity of constipation. 7-8. Prevalence and severity of diarrhea. 9-10. Prevalence and severity of fecal incontinence. 11-12. Prevalence and severity of rectal pain.

To be included, the study could not have reported only a composite outcome that shared a name with the outcome of interest. Examples of such composite outcomes included scales from the Gastrointestinal Symptom Rating Scale (GSRS; e.g. “abdominal pain” scale is the sum of items assessing (1) pain/discomfort in the upper abdomen, (2) hunger pains in the stomach, and (3) nausea). The only exceptions were functional GI disorders diagnosed according to the Rome criteria (see below). We did not include studies using proxy indicators to assess symptom prevalence, i.e. laxative use to assess constipation prevalence.

Secondary outcomes were as follows: 1. Prevalence of functional constipation. 2. Prevalence of each of the three stool consistency types. 3. Frequency of bowel movements (BMs). 4. Prevalence of functional diarrhea. 5. Prevalence of functional abdominal bloating/distension. 6. Prevalence of centrally mediated abdominal pain syndrome. 7. Prevalence of functional anorectal pain. 8. Associations/correlations between each of the lower GI symptoms/syndromes and health-related quality of life. 9. Associations/correlations between each of the lower GI symptoms/syndromes and

lab results. 10. Associations/correlations between each of the lower GI symptoms/syndromes and clinical data.

Stool consistency was classified as too hard (Bristol stool scale: types 1-2), normal (Bristol stool scale: types 3-5), or too loose (Bristol stool scale: types 6-7). Frequency of BMs was analyzed as a 4-level categorical variable: (1) less than three BMs per week, (2) at least three but less than seven BMs per week, (3) seven BMs per week (= once a day), (4) more than seven BMs per week (= more than once a day).

Design

We included observational studies, including case-control, cross-sectional, and cohort studies. Biographies, randomized controlled trials, reviews, meta-analyses, case reports, editorials, and studies protocols were excluded. Cross-sectional analysis of the baseline data from randomized controlled trials was permitted.

S2. Reporting bias assessment

To assess "reporting biases" such as selective non-publication (publication bias) and selective non-reporting of results, we conducted a Peters' regression test, calculated the Luis Furuya-Kanamori (LFK) index and generated both funnel and Doi plots for meta-analyses including at least 10 studies [1,2]. If asymmetry was detected, we reported whether it may have resulted from positive reporting bias (LFK index > 1; favoring studies that reported higher prevalence) or a negative one (LFK index < −1; favoring studies that reported lower prevalence). Calculations and plotting were done using functions from 'meta' (*metabias*, *funnel*) and 'metasens' (*lfkindex*, *doiplot*) R packages [3,4]. Since, as expected, included observational studies were rarely preceded by a published protocol, we did not plan nor perform comparison of planned and reported outcomes. Instead, in the case of data lacking, we tried to contact authors to obtain missing data.

S3. Confidence interval calculation, subgroup analysis, sensitivity analysis, and certainty assessment

Confidence intervals (95% CI) for individual study results of single proportions were estimated using the conservative exact Clopper–Pearson method. If data for multinomial proportions (e.g. symptom severity classified to at least 3 categories) were available from one study only, we estimated 95% CI with the Sison & Glaz method using *MultinomCI* function from 'DescTools' (version 0.99.44) R package [5].

In the case of both significant heterogeneity and at least 10 studies in the meta-analysis, we conducted pre-specified subgroup analyses [according to the date of data collection (before 2000, 2000-2010, after 2010), location of data collection (WHO Regions), age of participants, and sex of participants]. Performing subgroup analysis of meta-analysis with less than 10 studies would result in meaningless results due to too-low statistical power. Formal certainty assessment was not performed because there is no evidence-based tool for assessing studies of the prevalence of disease [6]. However, we followed the GRADE framework and underlined study limitations (RoB), inconsistency of results, imprecision, and reporting bias [7].

We conducted 7 sensitivity analyses for each single proportion (prevalence) outcome using the 'altmeta' package (version 3.3). Using *maprop.glmm* function, we tested how changing a logit transformation into another link [probit, cauchit, and complementary log-log links (cloglog)] would affect pooled prevalence estimation with GLMM [8]. Since a conventional two-step method to meta-analyze single proportion is still popular and the Freeman–Tukey double arcsine transformation (FTT) is the most widely used—yet controversial—to normalize proportion distribution before pooling [9,10], we used a *maprop.twostep* function with two methods of the between-study variance (ML, REML) and two ways of back-transformation [using the harmonic mean of the study-specific sample sizes ("harmonic" in tables) or the inverse of the synthesized result's variance as the overall sample size ("inverse var" in tables)] [8,9].

Supplementary Results

S1. Study characteristics

The vast majority of studies reported data collected for CKD G4-5 subgroup. Information for this subgroup was extracted from 30 studies, and nearly a half of them (14 studies) presented the cause of CKD. Mean/median age in the studies for CKD G4-5 subgroups ranged from 50 up to 83 years (on average: 66.6), while males consisted of 39-77% (on average: 59.6%) participants. Data on symptoms in patients with CKD G3 were extracted from 10 studies [11–20]. Mean/median age in these studies ranged from 56 up to 81 (on average 63.5), and males represented 52-83% (on average 64.4%) participants. We found far fewer studies reporting data on GI symptomatology in the early stages of CKD: data for the CKD G1-2 subgroup was extracted from 6 studies only [11–13,18–20]. Mean age in these studies ranged from 50 up to 66 (on average 55), while males represented 32-100% (on average 62.7%) participants. Cause of CKD was reported only in one study in this subgroup [20].

S2. Abdominal pain in ADPKD and Fabry disease

We suspected identifying more studies assessing the prevalence of abdominal pain in such diseases as ADPKD and Fabry disease. However, we had to exclude a number of identified studies, mainly due to them reporting composite outcomes (e.g. “lumbar and/or abdominal pain” instead of abdominal pain in ADPKD) or not presenting analysis for the non-dialysis CKD subgroup (aggregated data of Fabry disease patients with normal and abnormal kidney function). In a study conducted in Turkey, four out of seven [57.1% (95% CI 18.4 to 90.1%)] male patients with CKD caused by Fabry disease reported abdominal pain. Interestingly, none out of four female patients reported the symptom. We show extracted data on abdominal pain for ADPKD in the Supplementary Table S18.

Table S1. Deviations from the registered protocol with justification

Protocol	Current version	Justification
Additional outcome(s): (…) 2. Prevalence of having stool form suggesting constipation (Bristol stool scale: types 1-2). (…) 6. Prevalence of having stool form suggesting diarrhea (Bristol stool scale: types 6-7).	Secondary outcomes were as follows: (…) 2. Prevalence of three stool consistency types. (…) Stool consistency was classified as too hard (Bristol stool scale: types 1-2), normal (Bristol stool scale: types 3-5), or too loose (Bristol stool scale: types 6-7).	These 2 outcomes are supposed to be correlated, therefore both would be dependent effects sizes. To obtain unbiased results, we decided to meta-analyze stool consistency as a 3-level categorical variable.
Additional outcome(s): (…) 3. Prevalence of having less than 7 bowel movements per week. 4. Prevalence of having less than 3 bowel movements per week.	Secondary outcomes were as follows: (…) 3. Frequency of bowel movements (BMs). (…) Frequency of BMs was analyzed as a 4-level categorical variable: (1) less than three BMs per week, (2) at least three but less than seven BMs per week, (3) seven BMs per week (= once a day), (4) more than seven BMs per week (= more than once a day).	These 2 outcomes are supposed to be correlated, therefore both would be dependent effects sizes. To obtain unbiased results, we decided to meta-analyze bowel movement frequency as a 4-level categorical variable.
Sensitivity analysis [*of single proportion outcomes*] will be conducted using a random-effects meta-analysis with the Freeman-Tukey double arcsine transformation of proportions.	We conducted 7 sensitivity analyses for each single proportion (prevalence) outcome using 'altmeta' package (version 3.3). Using maprop.glmm function, we tested how changing a logit transformation into another link (probit, cauchit, and cloglog) would affect pooled prevalence estimation with GLMM. Since a conventional two-step method to meta-analyze single proportion is still popular and the Freeman–Tukey double arcsine transformation (FTT) is the most widely used—yet controversial—to normalize proportion distribution before pooling, we used the maprop.twostep function with two methods of the between-study variance (ML, REML) and two ways of back-transformation (using the harmonic mean of the study-specific sample sizes or the inverse of the synthesized result's variance as the overall sample size).	Justified in the "current version".
[*not mentioned*]	To assess "reporting biases" such as selective non-publication (publication bias) and selective non-reporting of results, we calculated the Luis Furuya-Kanamori (LFK) index and generated both funnel and Doi plots for meta-analyses including at least 5 studies. If asymmetry was detected, we planned to report whether it may have resulted from positive reporting bias (LFK index > 1; favoring studies that reported higher prevalence) or negative one (LFK index < −1; favoring studies that reported lower prevalence). Since, as expected, included observational studies were rarely preceded by a published protocol, we did not plan nor perform comparison of planned and reported outcomes. Instead, in case of data lacking, we tried to contact authors to obtain missing data.	Reporting biases were planned. However, since PROSPERO does not require a description of reporting bias assessment, this description was omitted from the original version of the protocol.
For each of the outcome, the following variables will be extracted from each paper: (…) [outcomes] in groups according to GFR (GFR higher than 60; GFR 30-60; GFR below 30; GFR below 15 mL/min/1.73 m^2) and according to albuminuria/UACR (below 30; 30-300; above 300 mg/24 h or mg/g). (…) Data that used the same (or enough similar) definition of symptom will be synthesized when available from at least 2 studies.	Since the burden of disease- and treatment-related symptoms increases with progression of CKD, we decided to meta-analyze all outcomes separately in the subgroups as follows: early CKD (G1 and G2, i.e. eGFR ≥ 60 mL/min per 1.73 m2), moderate CKD (G3, i.e. eGFR 30–59 mL/min per 1.73 m2), advance CKD (G4 and G5, i.e. eGFR < 30 mL/min per 1.73 m2).	While the separate analyses for each eGFR group were pre-planned and expressed in the "Data extraction (selection and coding)" section, we unintentionally omitted the direct statement in the "Strategy for data synthesis" / "Analysis of subgroups or subsets" sections.
Subgroup analyses by the presence of albuminuria, CKD etiology, date of data collection (before 2000, 2000-2010, after 2010), location of data collection, race/ethnicity, age group will be performed with the test for difference between the groups.	We planned to conduct separate meta-analyses according to albuminuria categories; however, data on albuminuria was not reported in the included studies. (…) We did not conduct pre-specified subgroup analyses to explore possible causes of heterogeneity among study results because of the too-small number of those studied, that would cause a too-low statistical power.	Justified in the "current version".

[*not mentioned*]	To compare the prevalence between subgroups, meta-analysis of within-study odds ratios was conducted using random effects model with restricted maximum-likelihood (REML) estimator for τ^2.	Subgroup effects are more credible if the comparison is made within rather than between studies with different methodological qualities, geographic localization, etc. The analysis was not pre-planned but requested during peer review.

Table S2. Search strategy

Database	Search
MEDLINE (via PubMed)	**#1** (chronic kidney[tw] OR chronic renal[tw] OR chronic glomerul*[tw] OR chronic nephro*[tw] OR progressive kidney[tw] OR progressive glomerul*[tw] OR progressive nephro*[tw] OR diabetic kidney[tw] OR diabetic renal[tw] OR diabetic glomerul*[tw] OR ckd[tw] OR esrd[tw] OR ((diabet*[tw] OR "Disease Progression"[mh:noexp] OR "Recurrence"[mh:noexp]) AND nephropath*[tw]) OR uremi*[tw] OR uraemi*[tw] OR proteinuri*[tw] OR nephrosclerosis[tw] OR glomerulosclerosis[tw] OR glomerular sclerosis[tw] OR "Glomerular Filtration Rate"[majr:noexp] OR microalbuminuri*[tw] OR macroalbuminuri*[tw] OR albuminuri*[tw] OR calciphylaxis[tw] OR secondary hyperparathyroidism[tw] OR "Hyperparathyroidism, Secondary"[mh:noexp] OR tubulointerstitial fibrosis[tw] OR interstitial fibrosis[tw] OR renal fibrosis[tw] OR kidney fibrosis[tw] OR vascular calcification*[tw] OR alport*[tw] OR denys-drash[tw] OR glomerulopathy[tw] OR hypoalbuminemi*[tw] OR hypoalbuminaemi*[tw] OR multicystic kidney*[tw] OR polycystic kidney*[tw] OR cystic kidney*[tw] OR kidney disease*[tw] OR kidney failur*[tw] OR kidney function*[tw] OR kidney insufficienc*[tw] OR kidney disorder*[tw] OR kidney dysfunction[tw] OR renal disease*[tw] OR renal failur*[tw] OR renal function*[tw] OR renal insufficienc*[tw] OR renal disorder*[tw] OR renal dysfunction[tw] OR ((kidney[tw] OR renal[tw]) AND (ckf[tw] OR crd[tw] OR crf[tw] OR eskd[tw] OR eskf[tw] OR esrf[tw] OR hyperparathyroidism[tw] OR end-stage[tw] OR endstage[tw] OR eGFR[tiab])) OR ((kidney transplant*[tiab] OR renal transplant*[tiab]) AND (candidates[tiab] OR wait list*[tiab] OR waiting list*[tiab])) OR ((ureteral obstruction[tw] OR nephritis OR glomerulonephritis OR nephrop* OR (obstruct*[tiab] AND (kidney*[tiab] OR renal[tiab] OR nephropathy[tiab]))) AND (sclerosi*[tw] OR fibrosi*[tw] OR fibrotic[tw]))) **#2** "Abdominal Pain"[MeSH Terms] OR "abdominal pai*"[Title/Abstract] OR "abdomen pai*"[Title/Abstract] OR "pain in abdomen"[Title/Abstract] OR "painful abdom*"[Title/Abstract] OR "Flatulence"[MeSH Terms] OR "flatulen*"[Title/Abstract] OR "bloated"[Title/Abstract] OR "bloating"[Title/Abstract] OR "diarrhea"[MeSH Terms] OR "diarrh*"[Title/Abstract] OR "loose stoo*"[tiab] OR "fecal incontinence"[MeSH Terms] OR "Encopresis"[Mesh] OR "faecal incontinenc*"[Title/Abstract] OR "fecal incontinenc*"[Title/Abstract] OR "bowel incontinenc*"[Title/Abstract] OR "constipation"[MeSH Terms] OR "constipat*"[Title/Abstract] OR "obstipation"[Title/Abstract] OR "rectal pain"[Title/Abstract] OR "anorectal pain"[Title/Abstract] OR "functional anorectal"[tiab] OR

	"defecation"[MeSH Terms] OR "defaecat*"[Title/Abstract] OR "defecat*"[Title/Abstract] OR "bowel movemen*"[All Fields] OR "Bristol Stool Form"[tiab] OR "Bristol Stool Scale"[tiab] OR BSFS[tiab] OR “gastrointestinal symptom*”[tiab] **#3** #1 AND #2 NOT ("animals"[mesh] NOT "humans"[mesh]) NOT ("animals"[mesh] NOT "humans"[mesh]) NOT (("infant"[MeSH Terms] OR "child"[MeSH Terms] OR "adolescent"[MeSH Terms]) NOT "adult"[MeSH Terms]) NOT ("Review"[Publication Type] OR "systematic review"[Publication Type] OR "Network Meta-Analysis"[MeSH Major Topic] OR "case reports"[Publication Type] OR "editorial"[Publication Type] OR "biography"[Publication Type] OR "Randomized Controlled Trial"[Publication Type] OR "Clinical Trial Protocol"[Publication Type]) NOT ("A Case Series"[Title] OR "systematic review and meta-analysis"[Title] OR "randomized clinical trial"[Title])
OpenDissertations (via EBSCO)	**#1** "chronic kidney" OR "chronic renal" OR "chronic glomerul*" OR "chronic nephro*" OR "progressive kidney" OR "progressive glomerul*" OR "progressive nephro*" OR "diabetic kidney" OR "diabetic renal" OR "diabetic glomerul*" OR ckd OR esrd OR (diabet* AND nephropath*) OR uremi* OR uraemi* OR proteinuri* OR nephrosclerosis OR glomerulosclerosis OR "glomerular sclerosis" OR "Glomerular Filtration Rate" OR microalbuminuri* OR macroalbuminuri* OR albuminuri* OR calciphylaxis OR "secondary hyperparathyroidism" OR "tubulointerstitial fibrosis" OR "interstitial fibrosis" OR "renal fibrosis" OR "kidney fibrosis" OR "vascular calcification*" OR alport* OR denys-drash OR glomerulopathy OR hypoalbuminemi* OR hypoalbuminaemi* OR "multicystic kidney*" OR "polycystic kidney*" OR "cystic kidney*" OR "kidney disease*" OR "kidney failur*" OR "kidney function*" OR "kidney insufficienc*" OR "kidney disorder*" OR "kidney dysfunction" OR "renal disease*" OR "renal failur*" OR "renal function*" OR "renal insufficienc*" OR "renal disorder*" OR "renal dysfunction" OR ((kidney OR renal) AND (ckf OR crd OR crf OR eskd OR eskf OR esrf OR hyperparathyroidism OR end-stage OR endstage OR eGFR)) OR (("kidney transplant*" OR "renal transplant*") AND (candidates OR "wait list*" OR "waiting list*")) OR (("ureteral obstruction" OR nephritis OR glomerulonephritis OR nephrop* OR (obstruct* AND (kidney* OR renal OR nephropathy))) AND (sclerosi* OR fibrosi* OR fibrotic))) **#2** #1 AND ("Abdominal Pain" OR "abdominal pai*" OR "abdomen pai*" OR "pain in abdomen" OR "painful abdom*" OR flatulen* OR bloated OR bloating OR diarrhea OR diarrh* OR "loose stoo*" OR "fecal incontinence" OR "faecal incontinenc*" OR "fecal incontinenc*" OR "bowel incontinenc*" OR constipation OR constipat* OR obstipation OR "rectal pain" OR "anorectal pain" OR "functional anorectal" OR defecation OR defaecat* OR defecat* OR "bowel movemen*" OR "Bristol Stool Form" OR "Bristol Stool Scale" OR BSFS OR "gastrointestinal symptom*")
Scopus	TITLE-ABS-KEY("chronic kidney") OR TITLE-ABS-KEY("diabetic kidney") OR TITLE-ABS("advanced kidney") OR TITLE-ABS("end stage renal") OR TITLE-ABS("endstage renal") OR TITLE-ABS("end stage kidney") OR TITLE-ABS-KEY("uremic patient*") OR TITLE-ABS-KEY("uraemic patient*") OR TITLE("kidney disease") OR TITLE("renal disease") OR TITLE-ABS("kidney insufficiency") OR TITLE-ABS("renal insufficiency") OR TITLE-ABS("ckd") OR TITLE-ABS("chronic renal") OR TITLE-ABS("progressive kidney") OR TITLE-ABS("progressive uremi*") OR TITLE-ABS("progressive uraemi*") OR (TITLE("chronic*") AND (TITLE("uremi*") OR TITLE("uraemi*"))) OR TITLE-ABS("nephrosclerosis") OR TITLE("glomerulosclerosis") OR TITLE("glomerular sclerosis") OR TITLE-ABS("macroalbuminuri*") OR TITLE-ABS("Renal Osteodystrophy") OR TITLE-ABS("kidney fibrosis") OR TITLE-ABS("renal fibrosis") OR TITLE-ABS("interstitial fibrosis") OR TITLE-ABS("renal hyperparathyroidism") OR TITLE("polycystic kidney*") OR ((TITLE-ABS-KEY("kidney") OR TITLE-ABS-KEY("renal")) AND (TITLE-ABS-KEY("ckf") OR TITLE-ABS-KEY("crd") OR TITLE-ABS-KEY("crf") OR TITLE-ABS-KEY("eskd") OR TITLE-ABS-KEY("eskf") OR TITLE-ABS-KEY("esrf") OR TITLE-ABS-KEY("esrd"))) OR ((TITLE-ABS-KEY("chronic*") OR TITLE-ABS-KEY("severe")) AND (TITLE-ABS-KEY("azotemia") OR TITLE-ABS-KEY("azotaemia"))) OR (TITLE("diabet*") AND (TITLE("nephropath*") OR TITLE("microalbuminuri*") OR TITLE("macroalbuminuri*") OR TITLE("albuminuri*"))) AND (

	TITLE-ABS ("abdominal pai*") OR TITLE-ABS-KEY ("abdomen pai*") OR TITLE-ABS ("pain in abdomen") OR TITLE-ABS ("painful abdom*") OR TITLE-ABS-KEY ("flatulen*") OR TITLE-ABS ("bloated") OR TITLE-ABS ("bloating") OR TITLE-ABS-KEY ("diarrh*") OR TITLE-ABS ("loose stoo*") OR TITLE-ABS-KEY ("faecal incontinenc*") OR TITLE-ABS-KEY ("fecal incontinenc*") OR TITLE-ABS-KEY ("bowel incontinenc*") OR TITLE-ABS-KEY ("constipat*") OR TITLE-ABS-KEY ("obstipation") OR TITLE-ABS-KEY ("rectal pain") OR TITLE-ABS-KEY ("anorectal pain") OR TITLE-ABS ("functional anorectal") OR TITLE-ABS ("defaecat*") OR TITLE-ABS ("defecat*") OR TITLE-ABS ("bowel movemen*") OR TITLE-ABS-KEY ("Bristol Stool Form") OR TITLE-ABS-KEY ("Bristol Stool Scale") OR TITLE-ABS ("BSFS") OR TITLE-ABS ("gastrointestinal symptom*") AND NOT (TITLE ("a case series") OR TITLE ("case report") OR TITLE ("systematic review and meta-analysis") OR TITLE ("randomized clinical trial") OR TITLE-ABS ("ClinicalTrials.gov") OR TITLE ("A randomized trial") OR TITLE ("randomized placebo-controlled trial") OR TITLE ("Efficacy and Safety of") OR TITLE ("a protocol of") OR TITLE ("meta-analysis of randomized"))) AND (EXCLUDE (DOCTYPE,"re") OR EXCLUDE (DOCTYPE,"ed"))
Web of Science (WoS; in all cases below)	#1 TS=("chronic kidney" OR "chronic renal" OR "chronic glomerul*" OR "chronic nephro*" OR "progressive kidney" OR "progressive glomerul*" OR "progressive nephro*" OR "diabetic kidney" OR "diabetic renal" OR "diabetic glomerul*" OR ckd OR esrd OR (diabet* AND nephropath*) OR uremi* OR uraemi* OR proteinuri* OR nephrosclerosis OR glomerulosclerosis OR "glomerular sclerosis" OR "Glomerular Filtration Rate" OR microalbuminuri* OR macroalbuminuri*

	OR albuminuri* OR calciphylaxis OR "secondary hyperparathyroidism" OR "tubulointerstitial fibrosis" OR "interstitial fibrosis" OR "renal fibrosis" OR "kidney fibrosis" OR "vascular calcification*" OR alport* OR denys-drash OR glomerulopathy OR hypoalbuminemi* OR hypoalbuminaemi* OR "multicystic kidney*" OR "polycystic kidney*" OR "cystic kidney*" OR "kidney disease*" OR "kidney failur*" OR "kidney function*" OR "kidney insufficienc*" OR "kidney disorder*" OR "kidney dysfunction" OR "renal disease*" OR "renal failur*" OR "renal function*" OR "renal insufficienc*" OR "renal disorder*" OR "renal dysfunction" OR ((kidney OR renal) AND (ckf OR crd OR crf OR eskd OR eskf OR esrf OR hyperparathyroidism OR end-stage OR endstage OR eGFR)) OR (("kidney transplant*" OR "renal transplant*") AND (candidates OR "wait list*" OR "waiting list*")) OR (("ureteral obstruction" OR nephritis OR glomerulonephritis OR nephrop* OR (obstruct* AND (kidney* OR renal OR nephropathy))) AND (sclerosi* OR fibrosi* OR fibrotic))) #2 TS=("Abdominal Pain" OR "abdominal pai*" OR "abdomen pai*" OR "pain in abdomen" OR "painful abdom*" OR flatulen* OR bloated OR bloating OR diarrhea OR diarrh* OR "loose stoo*" OR "fecal incontinence" OR "faecal incontinenc*" OR "fecal incontinenc*" OR "bowel incontinenc*" OR constipation OR constipat* OR obstipation OR "rectal pain" OR "anorectal pain" OR "functional anorectal" OR defecation OR defaecat* OR defecat* OR "bowel movemen*" OR "Bristol Stool Form" OR "Bristol Stool Scale" OR BSFS OR "gastrointestinal symptom*") #3 TI = ("Case Series" OR “case report” OR "systematic review and meta-analysis" OR “meta-analysis of randomized” OR “network meta-analysis” OR "randomized clinical trial" OR "randomized placebo-controlled trial" OR "randomized trial" OR “protocol for” OR “protocol of”) #4 #1 AND #2 NOT #3
WoS Core Collection (A&HCI, BKCI-SSH, BKCI-S, CCR-EXPANDED, ESCI, CPCI-SSH, CPCI-S, SCI-EXPANDED, SSCI)	#5 #4 **Refined by:** [excluding] **DOCUMENT TYPES:** (REVIEW OR EDITORIAL MATERIAL)
WoS SciELO	#5 #4 **Refined by**: [excluding] **DOCUMENT TYPES:** (REVIEW ARTICLE OR CASE REPORT)
WoS Korean Journal Database	#4

Table S3. Symptom questionnaires used for forward citation chasing

Group of questionnaires (date of citation chasing)	Name of questionnaire	DOI
Questionnaires not dedicated to CKD population (14-11-2021)	1. The memorial symptom assessment scale short form (MSAS-SF)	10.1002/1097-0142(20000901)89:5<1162::aid-cncr26>3.0.co;2-y
	2. The Condensed Memorial Symptom Assessment Scale (CMSAS)	10.1081/cnv-200026487
	3. The Memorial Symptom Assessment Scale (MSAS)	10.1016/0959-8049(94)90182-1
	4. Autonomic Symptom Profile (ASP)	10.1212/WNL.52.3.523
	5. The Palliative Care Outcome Scale (POS)	10.1136/qshc.8.4.219
	6. Integrated Palliative care Outcome Scale	10.1177/0269216315608348,
	7. Gastrointestinal Quality of Life Index	10.1002/bjs.1800820229
	8. Constipation Assessment Scale	10.1097/00002820-198906000-00012
	9. Patient Assessment of Constipation Symptoms	10.1080/003655299750025327
	10. Obstructed Defecation Syndrome Score	10.1111/j.1463-1318.2007.01262.x
	11. The NIH Patient-Reported Outcomes Measurement Information System (PROMIS) Gastrointestinal Symptom Scales	10.1038/ajg.2014.237
	12. Upper gastrointestinal disorders-symptom severity index (PAGI-SYM)	10.1007/s11136-004-9567-x
	13. Rome IV Diagnostic Questionnaire	10.1053/j.gastro.2016.02.014
	14-15. Rome III Diagnostic Questionnaires	10.5056/jnm14045, 10.1053/j.gastro.2006.03.008
Questionnaires dedicated to CKD population (26-12-2021)	1. Dialysis Symptom Index	10.1681/ASN.2005020157
	2. Patient Outcome Scale-Renal (POS-Renal)	10.1159/000183177
	3. Integrated Palliative Outcome Score (IPOS)-renal	10.1016/j.jpainsymman.2018.04.006
	4. The CKD Symptom Burden Index (CKD SBI)	10.1111/jorc.12152

Table S4. Items of electronic extraction form

Category	Item
Design and study characteristics	study design
	First author name
	Journal name
	Geographic coverage (country)
	Study period and year of publication
	Exclusion criteria
Sample characteristics (extracted for each of the eGFR groups)	Gender (proportion of males; 0-100)
	Race/ethnicity (proportions)
	CKD etiology (proportions)
	Age
	Creatinine (serum)
	eGFR
	Albuminuria
	Proteinuria
	BMI
Outcome details (extracted for each of the outcomes)	Tool used to identify the outcome (name of the questionnaire)
	Min and max values for the numerical scales
	Was the outcome tested for correlation/association with quality of life? Describe.
	Was the outcome tested for correlation/association with lab tests? Describe.
	Was the outcome tested for correlation/association with clinical data? Describe.
	Is information about prevalence in the control group (without CKD) collected/available?
Risk of bias assessment	JBI Critical Appraisal Checklist for Studies Reporting Prevalence Data
Results (extracted for each of the eGFR groups and outcomes)	Total (N analyzed)
	The number of participants reporting the outcome (cases)
	Mean/median, SD/IQR, range for severity outcomes evaluated with numerical scales

Table S5. Excluded studies with reason

Title	year	journal	Volume (issue)	First author	Decision	Source of record*
A study of gastric emptying in chronic renal failure	1997	Journal of Association of Physicians of India	45 (11)	Alimchandani, A.	WRONG OUTCOME (fullness instead of bloating or abdominal pain)	DS
Application of immunosuppressants in patients with autosomal dominant polycystic kidney disease after kidney transplantation	2020	Nan fang yi ke da xue xue bao	40 (4)	Li, Q.	WRONG OUTCOME (aggregated data for all gastrointestinal symptoms such as nausea, vomiting, diarrhea, and flatulence)	DS
Association of Constipation with risk of end-stage renal disease in patients with chronic kidney disease.	2019	BMC nephrology	20 (1)	Lu CY	WRONG OUTCOME (registry-based)	DS
Associations between multimorbidity and glycaemia (HbA1c) in people with type 2 diabetes: Cross-sectional study in Australian general practice	2020	BMJ Open	10 (11)	Chiang, J.I.	WRONG OUTCOME (registry-based)	DS
Asymptomatic pyuria in diabetic women.	2001	Nippon Ika Daigaku zasshi	68 (5)	Nakano H	WRONG POPULATION (lack of separate analysis for diabetic nephropathy) and OUTCOME (constipation treatment instead of reporting symptom)	DS
Autonomic neuropathy is associated with increased cardiovascular risk factors: the EURODIAB IDDM Complications Study.	2002	Diabetic medicine	19 (11)	Kempler P	WRONG OUTCOME (nocturnal diarrhea instead of diarrhea) and POPULATION (lack of separate analysis for patients with diabetic nephropathy)	DS
Autosomal dominant polycystic kidney disease: MR imaging evaluation using current techniques	2003	Journal of Magnetic Resonance Imaging	18 (2)	Mosetti, M.A.	WRONG OUTCOME (indication for the magnetic resonance examination instead of patients' symptoms)	DS
Autosomal dominant polycystic kidney disease: observations from a university hospital in Saudi Arabia.	1995	Saudi journal of kidney diseases and transplantation	6 (1)	Al-Muhanna FA	WRONG OUTCOME (abdominal pain assessed based on retrospective medical records analysis only)	DS
Autosomal dominant polycystic kidney disease: Study of clinical characteristics in an Indian population.	2017	Saudi journal of kidney diseases and transplantation	28 (1)	Vikrant S	WRONG OUTCOME ("Lumbar or abdominal pain" instead of abdominal pain)	DS
Autosomal dominant polycystic kidney disease: symptoms and clinical findings.	1984	The Quarterly journal of medicine	53 (212)	Milutinovic J	WRONG OUTCOME ("back pain", "abdominal tenderness and fullness")	DS
Baseline graft status is a critical predictor of kidney graft failure after diarrhoea.	2019	Nephrology, dialysis, transplantation	34 (9)	Devresse A	WRONG POPULATION (only symptomatic patients, lack of subanalysis for outpatients)	DS
Burden of drug use for gastrointestinal symptoms and functional gastrointestinal disorders in France: a national study using reimbursement data for 57 million inhabitants.	2019	Therapeutic advances in gastroenterology	12	Tuppin P	WRONG POPULATION (dialysis aggregated with transplanted patients)	DS
Characteristics and Dysbiosis of the Gut Microbiome in Renal Transplant Recipients.	2020	Journal of clinical medicine	9 (2)	Swarte JC	WRONG OUTCOME (symptoms prevalence not assessed)	DS

Characteristics of the patients with diabetic nephropathy with relatively low serum creatinine at the initiation of dialysis.	1990	Nihon Jinzo Gakkai shi	32 (9)	Nakao T	WRONG OUTCOME (aggregated prevalence of gastrointestinal symptoms that was a reason for introduction dialysis)	DS
Characterization of Upper Gastrointestinal Symptoms, Gastric Motor Functions, and Associations in Patients with Diabetes at a Referral Center.	2019	The American journal of gastroenterology	114 (1)	Chedid V	WRONG POPULATION (lack of separate analysis for patients with diabetic nephropathy)	DS
Chronic constipation is negatively associated with colonic diverticula	2021	Scandinavian Journal of Gastroenterology	56 (11)	Higashimori, A.	WRONG POPULATION (lack of separate analysis for non-dialysis patients with CKD)	DS
Clinical and pathological spectrums of aristolochic acid nephropathy.	2012	Clinical nephrology	78 (1)	Chen D	WRONG POPULATION (both AKI and CKD) and WRONG OUTCOME (aggregated data on nausea, vomiting and poor appetite)	DS
Clinical factors associated with the symptoms of constipation in patients with diabetes mellitus: A multicenter study.	2018	Journal of gastroenterology and hepatology	33 (4)	Yamada E	WRONG POPULATION (lack of separate analysis for patients with diabetic nephropathy)	DS
Clinical Features of 167 Inpatients with Autosomal Dominant Polycystic Kidney Disease at a Single Center in China.	2018	Medical science monitor	24	Meng J	WRONG OUTCOME ("Lumbar and/or abdominal pain" and "flank pain" instead of abdominal pain)	DS
Clinical manifestations of autosomal dominant polycystic kidney disease in patients older than 50 years.	1990	American journal of kidney diseases	15 (3)	Milutinovic J	WRONG OUTCOME ("frequent or constant" back/abdominal tenderness after exclusion of "gastrointestinal and gynecological causes" was assessed instead of abdominal pain)	DS
Clinical manifestations, risk factors, and prognostic factors of cytomegalovirus enteritis.	2021	Gut pathogens	13 (1)	Yeh PJ	WRONG POPULATION (inpatients; CKD only in 31% of participants; lack of subgroup analysis)	DS
Clinical remarks on diarrhea and vomiting, the result of renal disease	1867	British Medical Journal	1 (330)	Johnson, G.	WRONG PUBLICATION TYPE (letter)	DS
Clinical study on thyroid function in chronic renal failure	1983	The Japanese Journal of Nephrology	25 (8)	Kijima, Y.	WRONG POPULATION (symptoms evaluated only amongst dialysis patients)	DS
Colonic changes in uremia	1981	Union Medicale du Canada	110 (5)	Caron, C.	WRONG POPULATION (both dialysis and non-dialysis ESKD patients)	DS
Colonic diverticular disease in autosomal dominant polycystic kidney disease: is there really an association? A nationwide analysis.	2021	International journal of colorectal disease	36 (1)	Duarte-Chavez R	WRONG OUTCOME (registry-based)	DS
Comorbidity and polypharmacy in chronic heart failure: A large cross-sectional study in primary care	2017	British Journal of General Practice	67 (658)	Baron-Franco, B.	WRONG OUTCOME (registry-based)	DS
Comorbidity Burden in Adults With Autism Spectrum Disorders and Intellectual Disabilities—A Report From the EFAAR (Frailty Assessment in Ageing Adults With Autism Spectrum and Intellectual Disabilities) Study	2019	Frontiers in Psychiatry	10	Miot, S.	WRONG POPULATION (not CKD)	DS

Comparison of High-Resolution Manometry in Patients Complaining of Dysphagia among Patients with or without Diabetes Mellitus.	2021	Digestion	102 (4)	Muroi K	WRONG POPULATION (lack of subgroup analysis for patients with diabetic nephropathy)	DS
Constipation In Chinese Elderly: A Hidden Cause Of Chronic Kidney Disease And The Risk Of Rapid Renal Function Decline	2020	Nephrology Dialysis Transplantation	35	Jian, GH	WRONG OUTCOME (registry based study; unclear definition of constipation)	DS
Constipation might be associated with risk of allergic rhinitis: A nationwide population-based cohort study.	2020	PloS one	15 (10)	Wu MC	WRONG OUTCOME (registry-based)	DS
Constipation, hard stools, fecal urgency, and incomplete evacuation, but not diarrhea is associated with diabetes and its related factors.	2016	World journal of gastroenterology	22 (11)	Ihana-Sugiyama N	WRONG SETTINGS (inpatients rather than outpatients)	DS
Conversion to mycophenolate mofetil in conjunction with stepwise withdrawal of cyclosporine in stable renal transplant recipients.	2000	Transplantation	69 (3)	Schrama YC	WRONG OUTCOME (instead of diarrhea/other symptoms prevalence assessment, only severe, probably MMF-associated, diarrhea cases were reported)	DS
Conversion to sirolimus-based maintenance immunosuppression using daclizumab bridge therapy in renal transplant recipients.	2004	Clinical transplantation	18	Sundberg AK	WRONG OUTCOME ("diarrhea" not defined; period prevalence of adverse effect instead of point prevalence of symptom)	DS
Correlation of Cognitive Impairment with Constipation and Renal Failure	2016	Sains Malaysiana	45 (9)	Eshkoor, SA	Wrong population ("renal failure" was "recorded based on both respondents report and physician's diagnosis"; lack of lab test or eGFR estimation)	DS
Cross-sectional study of quality of life and symptoms in chronic renal disease patients: The Modification of Diet in Renal Disease Study	1997	American Journal of Kidney Diseases	29 (6)	Rocco, M.V.	WRONG OUTCOME (Prevalence and severity of constipation, diarrhea, and abdominal bloating were assessed but not reported; authors reported "severity index score" (result of multiplication the frequency by the severity of each symptom") of abdominal bloating	DS
Cryptosporidium spp. Infection in Solid Organ Transplantation: The Nationwide "TRANSCRYPTO" Study.	2017	Transplantation	101 (4)	Lanternier F	WRONG POPULATION (mixed of kidney-, liver-, heart-, and pancreas-transplant patients)	DS
Decreased concentrations of deoxycholic acid in serum of uraemic patients with diarrhoea.	1990	Scandinavian journal of clinical and laboratory investigation	50 (3)	Stenvinkel P	WRONG POPULATION (mixed of 16 dialysis and 2 non-dialysis CKD patients)	DS
Delayed gastric emptying among Indian patients with non-diabetic chronic kidney disease	2021	Indian Journal of Nephrology	31 (2)	Kumar, M.S.	WRONG POPULATION (mix of both dialysis- and non-dialysis patients) and OUTCOME (GCSI subscale instead of 1-item symptom)	DS
Delayed gastric emptying in patients with chronic renal failure	1996	Nuclear Medicine Communications	17 (2)	Kao, C.H.	WRONG OUTCOME (aggregated presence of upper gastrointestinal symptoms was only reported)	DS
Delayed Gastric Emptying Is Associated With Early and Long-term Hyperglycemia in Type 1 Diabetes Mellitus.	2015	Gastroenterology	149 (2)	Bharucha AE	WRONG POPULATION (lack of separate analysis for patients with diabetic nephropathy)	DS

Demographic, diagnostic and therapeutic characteristics of autosomal dominant polycystic kidney disease in Ghana.	2021	BMC nephrology	22 (1)	Okyere P	WRONG POPULATION (both AKI and CKD)	DS
Diabetic factors associated with gastrointestinal symptoms in patients with type 2 diabetes.	2010	World journal of gastroenterology	16 (14)	Kim JH	WRONG POPULATION (lack of subgroup analysis for patients with diabetic nephropathy)	DS
Diarrhea In A Patient With Renal-Failure	1976	Minnesota Medicine	59 (1)	Tsai, SH	WRONG PUBLICATION TYPE (case report)	DS
Dietary intake and nutritional deficiencies in patients with diabetic or idiopathic gastroparesis.	2011	Gastroenterology	141 (2)	Parkman HP	WRONG POPULATION (lack of separate analysis for diabetic nephropathy)	DS
Dyspepsia among patients with chronic kidney disease: a cross sectional study.	2013	International archives of medicine	6 (1)	Bacci MR	WRONG OUTCOME (dyspepsia)	DS
Effect of tolerance versus chronic immunosuppression protocols on the quality of life of kidney transplant recipients.	2016	JCI insight	1 (8)	Madariaga ML	WRONG OUTCOME (prevalence of lower GI symptoms was not reported)	DS
Epigenetic Alterations Are Associated With Gastric Emptying Disturbances in Diabetes Mellitus.	2020	Clinical and translational gastroenterology	11 (3)	Puthanmadhom Narayanan S	WRONG POPULATION (lack of separate analysis for patients with diabetic nephropathy)	DS
Evaluation of E148Q and Concomitant AA Amyloidosis in Patients with Familial Mediterranean Fever.	2021	Journal of clinical medicine	10 (16)	Arici ZS	WRONG OUTCOME (unclear whether point or period prevalence was reported; unclear definition of symptoms/methods of assessment)	DS
Evaluation of tolerance and safety of conversion from mycophenolate mofetil to enteric-coated mycophenolic acid in renal transplant recipients.	2017	Journal of biological regulators and homeostatic agents	31 (1)	Qiao LW	WRONG POPULATION (only symptomatic kidney transplanted patients)	DS
Evaluation of upper gastrointestinal symptoms and effect of different modalities of treatment in patients of chronic kidney disease	2014	Journal, Indian Academy of Clinical Medicine	15 (3)	Nand, N.	WRONG POPULATION (only symptomatic patients) AND OUTCOME (lack of report of associations between abdominal pain and any clinical/lab findings)	DS
Exocrine pancreatic dysfunction is common in hepatocyte nuclear factor 1β-associated renal disease and can be symptomatic.	2018	Clinical kidney journal	11 (4)	Clissold RL	WRONG OUTCOME (aggregated data on abdominal pain, loose stools or unintentional weight loss)	DS
Familial Mediterranean fever in Mexico City. A 20-year follow-up.	2004	Cirugia y cirujanos	72 (2)	Halabe-Cherem J	WRONG POPULATION (lack of patients with chronic kidney disease	DS
Gastric emptying in chronic renal failure	1985	British Medical Journal (Clinical research ed.)	291 (6491)	McNamee, P.T.	WRONG OUTCOME (e.g., gastric emptying, nausea, vomiting)	DS
Gastric helicobacter and upper gastrointestinal symptoms in chronic renal failure	1991	Annals of Medicine	23 (4)	Ala-Kaila, K.	WRONG OUTCOME (even though "all renal patients were systematically questioned as to upper GI symptoms such as heartburn or upper gastric pain relieved by milk or antacids", prevalence of symptoms was not reported)	DS

Gastroduodenal lesions and Helicobacter pylori infection in dyspeptic patients with and without chronic renal failure	2005	Helicobacter	10 (1)	Nardone, G.	WRONG POPULATION (mixed non-dialysis and dialysis CKD patients)	DS
Gastroesophageal reflux disease in chronic renal failure patients: evaluation by endoscopic examination.	2009	The Tokai journal of experimental and clinical medicine	34 (3)	Kawaguchi Y.	WRONG OUTCOME (not detailed, "some upper GI symptoms")	DS
Gastrointestinal complications in patients with chronic kidney disease--a 5-year retrospective study from a tertiary referral center.	2013	Renal failure	35 (1)	Thomas R	WRONG POPULATION (only symptomatic CKD patients; hemodialysis patients mixed with non-transplanted CKD patients)	DS
Gastrointestinal symptoms and shock in a patient with chronic renal failure	1980	The American Journal of Medicine	69 (4)		WRONG PUBLICATION TYPE (case report)	DS
Gastrointestinal transit disorders in patients with insulin-treated diabetes mellitus.	1990	Digestive diseases (Basel, Switzerland)	8 (1)	Wegener M	WRONG POPULATION (lack of separate analysis for diabetic nephropathy) and SETTINGGS (inpatients)	DS
GASTROPATHIES IN PATIENTS WITH 3-4 STAGES OF CHRONIC KIDNEY DISEASE.	2016	Eksperimental'naia i klinicheskaia gastroenterologiia	(10)	Abdurakhmanova NM	WRONG OUTCOME (only upper gastrointestinal symptoms were evaluated)	DS
Genetic Polymorphisms Affecting Tacrolimus Metabolism and the Relationship to Post-Transplant Outcomes in Kidney Transplant Recipients.	2021	Pharmacogenomics and personalized medicine	14	Cheng F	WRONG OUTCOME (unclear definition and assessment of diarrhea)	DS
Health impact of acute intermittent porphyria in latent and non-recurrent attacks patients.	2021	Orphanet journal of rare diseases	16 (1)	Buendía-Martínez J	WRONG POPULATION (lack of subgroup analysis for 8 CKD patients)	DS
Helicobacter pylori eradication for the treatment of dyspeptic symptoms in chronic renal failure	2005	Annals of Saudi Medicine	25 (5)	Šimunić, M	WRONG OUTCOME (probably epigastric rather than abdominal pain)	DS
Henoch-Schönlein purpura in adults. a study of 40 cases	1996	Revue de Medecine Interne	17 (5)	Lasseur, C.	WRONG OUTCOME (unclear definition of diarrhea, probably based on medical records)	DS
Histomorphological patterns of renal amyloidosis: A correlation between histology and chemical type of amyloidosis	1997	Human Pathology	28 (7)	Looi, L.-M.	WRONG OUTCOME (GI symptoms not assessed in all patients)	DS
Immunoglobulin light chain amyloidosis is diagnosed late in patients with preexisting plasma cell dyscrasias.	2014	American journal of hematology	89 (11)	Kourelis TV	WRONG POPULATION (lack of subgroup analysis for CKD patients) and OUTCOME ("earliest referable symptom or abnormal laboratory value" instead of symptom prevalence)	DS
Impact of conversion to a once daily tacrolimus-based regimen in kidney transplant recipients with gastrointestinal complications.	2012	Transplantation	93 (9)	Veroux M	WRONG POPULATION (only symptomatic kidney transplanted patients)	DS

Impaired gastric motility and its relationship to gastrointestinal symptoms in patients with chronic renal failure.	2005	Journal of gastroenterology	40 (12)	Hirako M	WRONG OUTCOME (assessed but not reported: "All patients completed a self-administered questionnaire that included seven symptoms (anorexia, nausea, heartburn, abdominal pain, bloating, diarrhea, and constipation)")	DS
Improvement in autonomic and gastric function following pancreas-kidney versus kidney-alone transplantation and the correlation with quality of life.	1994	Transplantation	57 (6)	Hathaway DK	WRONG OUTCOME (abdominal pain and bloating assessed but reported as composite score of gastrointestinal symptoms)	DS
Incidence and Causes of Late Hospital Readmissions After Living Donor Renal Transplant: A Retrospective Study.	2021	Experimental and clinical transplantation	19 (5)	Sharma A	WRONG OUTCOME (diarrhea as a hospital admission reason)	DS
Increased prevalence of gastrointestinal symptoms in patients with chronic renal failure.	2000	Gastroenterology	118 (4)	Strid, H	WRONG OUTCOME (prevalence of GI symptoms not reported)	DS
Late conversion to mammalian target of rapamycin inhibitor/proliferation signal inhibitors in kidney transplant patients: clinical experience in the last 5 years.	2010	Transplantation proceedings	42 (8)	Sola E	WRONG OUTCOME (aggregated data on all gastrointestinal symptoms)	DS
Laxative Use and Change in Estimated Glomerular Filtration Rate in Patients With Advanced Chronic Kidney Disease.	2020	Journal of renal nutrition	31 (4)	Sumida K	WRONG OUTCOME (registry based)	DS
Laxative Use and Risk of Dyskalemia in Patients with Advanced CKD Transitioning to Dialysis.	2021	Journal of the American Society of Nephrology	32 (4)	Sumida K	WRONG OUTCOME (registry based)	DS
Laxative use in patients with advanced chronic kidney disease transitioning to dialysis.	2020	Nephrology, dialysis, transplantation	36 (11)	Sumida K	WRONG OUTCOME (registry based)	DS
Long-term outcome of live donor kidney transplantation for renal amyloidosis	2003	American Journal of Kidney Diseases	42 (2)	Sherif, A.M.	WRONG OUTCOME (aggregated data on nausea, vomiting, diarrhea, and abdominal pain)	DS
Long-term outcomes of lupus nephritis treated with regimens based on cyclophosphamide and mycophenolate mofetil	2020	Lupus	29 (8)	Prasad, N.	WRONG OUTCOME ("diarrhea" not defined; period prevalence of adverse effect instead of point prevalence of symptom)	DS
Microsporidia infection among various groups of the immunocompromised patients.	2018	Tropical biomedicine	35 (2)	Hassan NA	WRONG POPULATION (ESKD not specified - unclear whether there were dialysis patients included)	DS
Nephrological manifestations of patients with Fabry disease in Argentina	2007	Revista de Nefrologia, Dialisis y Trasplante	27 (3)	Marcelo Neumann, P	WRONG POPULATION (lack of subgroup analysis for non-dialysis CKD patients)	DS
Outcomes and Factors Associated With Reduced Symptoms in Patients With Gastroparesis.	2015	Gastroenterology	149 (7)	Pasricha PJ	WRONG POPULATION (lack of separate analysis for diabetic nephropathy)	DS
Pain patterns in patients with polycystic kidney disease	2004	Kidney International	66 (4)	Bajwa, Z.H.	WRONG POPULATION (aggregated data for both non-dialysis, dialysis, and post-transplant patients)	DS
Patients with chronic renal failure have abnormal small intestinal motility and a high prevalence of small intestinal bacterial overgrowth.	2003	Digestion	67 (3)	Strid H	WRONG POPULATION (mix of both dialysis- and non-dialysis patients)	DS
Prevalence and evaluation of symptoms in advanced chronic kidney disease	2015	Enfermeria Nefrologica	18 (3)	Gutiérrez Sánchez D	WRONG PUBLICATION TYPE (Review)	DS

Prevalence and pattern of cystic kidney diseases in Ilorin, Nigeria.	2010	Saudi journal of kidney diseases and transplantation	21 (6)	Chijioke, A.	WRONG OUTCOME (abdominal pain as a presenting feature, not a systematically assessed symptom) AND CONTEXT (inpatients)	DS
Prevalence and predictors of delayed gastric emptying among Indian patients with long-standing type 2 diabetes mellitus.	2016	Indian journal of gastroenterology	35 (5)	Anudeep V	WRONG POPULATION (lack of separate analysis for patients with diabetic nephropathy)	DS
Prevalence of amyloid deposition in long standing rheumatoid arthritis in Iranian patients by abdominal subcutaneous fat biopsy and assessment of clinical and laboratory characteristics.	2006	BMC musculoskeletal disorders	7	Alishiri GH	WRONG POPULATION (lack of separate analysis for CKD patients/patients with renal amyloidosis)	DS
Prevalence of Chronic Constipation and Chronic Diarrhea in Diabetic Individuals in the United States.	2019	The American journal of gastroenterology	114 (1)	Sommers T	WRONG POPULATION (Diabetic patients. Neither creatinine nor proteinuria was collected. CKD was defined as "Told you had weak/failing kidneys")	DS
Prevalence of diarrhea in end-stage renal disease patients initiating hemodialysis	2021	Renal Replacement Therapy	7 (1)	Oba, M.	WRONG POPULATION (inpatients with both acute and chronic kidney disease)	DS
Prevalence of gastrointestinal symptoms in patients with chronic obstructive pulmonary disease.	2008	European journal of gastroenterology & hepatology	20 (4)	Niklasson A	WRONG OUTCOME (GSRS subscale instead of symptom)	DS
Prevalence of gastrointestinal symptoms in young and middle-aged diabetic patients.	1999	Scandinavian journal of gastroenterology	34 (12)	Spångéus A	WRONG POPULATION (lack of reported separate analysis for diabetic nephropathy)	DS
Prevalence of Helicobacter pylori in patients with different renal function	1997	Turkish Journal of Gastroenterology	8 (3)	Vardar, R.	WRONG OUTCOME (lack of data on the symptom prevalence)	DS
Prevalence of Intestinal Protozoa among Saudi Patients with Chronic Renal Failure: A Case-Control Study.	2015	Journal of tropical medicine	2015	Hawash YA	WRONG POPULATION (it is not clear whether dialysis patients were included)	DS
Prevalence of symptoms in female Fabry disease patients: a case-control survey.	2012	Journal of inherited metabolic disease	35 (5)	Bouwman MG	WRONG POPULATION (lack of information about chronic kidney disease)	DS
Prevalence of the need for sodium intake restriction and the use of laxatives in palliative patients	2018	Revista Espanola de Enfermedades Digestivas	110 (11)	Gándara-Del-Castillo, Á.	WRONG POPULATION (mixed of CKD and other palliative patients) and WRONG OUTCOME (laxative usage)	DS
Primary IgA glomerulonephritis and Schönlein-Henoch purpura nephritis: Clinicopathological and immunohistological characteristics.	1978	The Quarterly journal of medicine	47 (188)	Nakamoto Y	WRONG OUTCOME (only "abdominal pain" evaluated based on medical records)	DS
Quality of life in renal transplant recipients following conversion from mycophenolate mofetil to enteric-coated mycophenolate sodium.	2007	Transplantation proceedings	39 (7)	Cofan F	WRONG POPULATION (only symptomatic kidney transplanted patients)	DS
Racial differences in symptoms and complications in adults with type 2 diabetes mellitus.	1999	Ethnicity & health	4 (1)	Konen JC	WRONG POPULATION (lack of separate analysis for diabetic nephropathy)	DS
Renal function and symptoms/adverse effects in opioid-treated patients with cancer.	2015	Acta anaesthesiologica Scandinavica	59 (8)	Kurita GP	WRONG POPULATION (advance cancer population)	DS

Retrospective analysis of the overt proteinuria diabetic kidney disease in the treatment of modified Shenzhuo formula for 2 years	2017	Medicine (United States)	96 (12)	Chen, H	WRONG OUTCOME (prevalence of "chief complaint"/"the main symptoms of interrogation" were evaluated instead of systematic assessment of lower GI symptoms)	DS
Role of Endoscopic Findings and Biopsies in Renal Transplant Recipients With Gastrointestinal Complications: A Tertiary Care Experience.	2018	Experimental and clinical transplantation	16 (5)	Wadhwa RK	WRONG OUTCOME (diarrhea as an indication for endoscopy, not as a symptom; aggregated endoscopy findings independently of indication)	DS
Safety of Eplerenone for Kidney-Transplant Recipients with Impaired Renal Function and Receiving Cyclosporine A.	2016	PloS one	11 (4)	Bertocchio JP	WRONG OUTCOME (gastrointestinal symptoms were not systematically assessed)	DS
Saliva Composition And Upper Gastrointestinal Symptoms In Chronic Renal Disease	2012	NEPHROLOGY	17	Manley, K	WRONG OUTCOME (only upper gastrointestinal symptoms)	DS
Screening for celiac disease among patients with chronic kidney disease.	2012	Renal failure	34 (5)	Sahin I	WRONG OUTCOME (prevalence of symptoms were not assessed)	DS
Serum-Mediated Inhibition of Enzyme Replacement Therapy in Fabry Disease.	2016	Journal of the American Society of Nephrology : JASN	27 (1)	Lenders M	WRONG POPULATION (mixed of non-dialysis, dialysis, and transplanted patients)	DS
Signs and symptoms in chronic renal failure. II. Vomiting, twitching, haemorrhagic diathesis, convulsions, itching, and diarrhoea.	1958	Acta medica Scandinavica	160 (5)	Effersoe P	WRONG PUBLICATION TYPE (case series)	DS
Study of live donor kidney transplantation outcome in recipients with renal amyloidosis.	1994	Nephrology, dialysis, transplantation	9 (6)	Sobh M	WRONG OUTCOME (aggregated data on nausea, vomiting, abdominal pains and diarrhoea)	DS
Symptom-Based Stratification of Diabetes Mellitus by Renal Function Decline (SYSTEM): A Retrospective Cohort Study and Modeling Assessment.	2021	Frontiers in medicine	8	Chan KW	WRONG POPULATION (lack of subanalysis for patients with CKD/diabetic nephropathy) and OUTCOME ("Abdominal distension" instead of bloating; "Alternating dry or loose stool" instead of constipation/diarrhea)	DS
Taste genetics and gastrointestinal symptoms experienced in chronic kidney disease.	2015	European journal of clinical nutrition	69 (7)	Manley KJ	WRONG OUTCOME ("dry mouth, taste changes, nausea, dry retching and vomiting")	DS
The association of combined total kidney and liver volume with pain and gastrointestinal symptoms in patients with later stage autosomal dominant polycystic kidney disease	2017	American Journal of Nephrology	46 (3)	D'Agnolo, H.M.A.	WRONG OUTCOME (upper and lower abdominal pain assessed separately)	DS
The clinical features and outcomes of systemic AL amyloidosis: A cohort of 231 Chinese patients	2015	Clinical Kidney Journal	8 (1)	Huang, X.	WRONG POPULATION (lack of separate analysis for patients with CKD) and WRONG OUTCOME ("recurrent diarrhea" instead of diarrhea)	DS
The Gastrointestinal-Tract In Uremia	1993	Digestive Diseases And Sciences	38 (2)	Kang, JY	WRONG PUBLICATION TYPE (narrative review)	DS
The impact of gastroesophageal reflux disease, irritable bowel syndrome, and functional constipation on health-related quality of life in patients with chronic kidney disease	2018	Journal Of Gastroenterology And Hepatology	33	Nor, NM	WRONG POPULATION (mixed with dialysis patients)	DS

The prevalence of gastrointestinal symptoms in patients with chronic renal failure is increased and associated with impaired psychological general well-being	2002	Nephrology Dialysis Transplantation	17 (8)	Strid, H.	WRONG OUTCOME (GSRS subscale instead of symptom)	DS
Tolerability of mycophenolate sodium in renal transplant recipients	2018	International Journal of Clinical Pharmacy	40 (6)	Hiramoto, L.L.	WRONG OUTCOME (diarrhea as one of the reason for mycophenolate dose change, not evaluated as a symptom)	DS
Unilateral multicystic renal disease in adults	1982	Journal of Urology	128 (2)	Ambrose, S.S.	WRONG PUBLICATION TYPE (case series)	DS
Upper gastro-intestinal mucosal changes in patients with chronic renal failure.	1989	The Journal of the Association of Physicians of India	37 (9)	Goenka MK	WRONG OUTCOME (prevalence of nausea, vomiting, anorexia and GI bleeding was reported)	DS
Uraemic Diarrhea.	1869	British medical journal	2 (464)	Forthergill JM	WRONG PUBLICATION TYPE (letter)	DS
Uremia And Abdominal Pain	1968	Postgraduate Medicine	44 (4)	Donnelly, WJ	WRONG PUBLICATION TYPE (case report)	DS
Uremigenic diarrheas.	1957	Acta gastro-enterologica Belgica	20 (11)	Froehlich AL	WRONG PUBLICATION TYPE (case series)	DS
Validation of the IPOS-Renal Symptom Survey in Advanced Kidney Disease: A Cross-sectional Study	2018	Journal of Pain and Symptom Management	56 (2)	Raj, R.	WRONG POPULATION (lack of separate analysis for non-dialysis patients)	DS
Variable clinical features of patients with Fabry disease and outcome of enzyme replacement therapy	2021	Molecular Genetics and Metabolism Reports	26	Dutra-Clarke, M.	WRONG POPULATION (lack of separate analysis for patients with CKD) and OUTCOME (aggregated abdominal pain, constipation, and diarrhea)	DS
CKD in Elderly Patients Managed without Dialysis: Survival, Symptoms, and Quality of Life	2015	Clinical journal of the American Society of Nephrology	10 (2)	Brown, Mark A.	WRONG OUTCOME (prevalence not reported)	CCQ (not dedicated to CKD)
Delayed gastric emptying associates with diabetic complications in diabetic patients with symptoms of gastroparesis	2019	The American journal of gastroenterology	114 (11)	Parkman, Henry P.	WRONG POPULATION (only symptomatic patients)	CCQ (not dedicated to CKD)
Delayed Gastric Emptying Is Associated With Early and Long-term Hyperglycemia in Type 1 Diabetes Mellitus.	2015	Gastroenterology	149 (2)	Bharucha, A.E.	WRONG POPULATION (lack of separate analysis for patients with diabetic nephropathy)	CCQ (not dedicated to CKD)
Development and validation of a specific questionnaire for evaluating the impact of gastrointestinal symptoms on the health-related quality of life of transplant patients.	2012	Transplantation proceedings	44 (5)	Ortega, F.	WRONG POPULATION (patients after transplantation of different organs) and OUTCOME (prevalence not reported)	CCQ (not dedicated to CKD)
Epigenetic Alterations Are Associated With Gastric Emptying Disturbances in Diabetes Mellitus.	2020	Clinical and translational gastroenterology	11 (3)	Narayanan, S.P.	WRONG POPULATION (lack of separate analysis for patients with diabetic nephropathy)	CCQ (not dedicated to CKD)
Factors affecting diabetic patient's long-term quality of life after simultaneous pancreas-kidney transplantation: a single-center analysis.	2021	Langenbeck's archives of surgery	406 (3)	López-Sánchez, J.	WRONG OUTCOME (GI symptoms prevalence were not assessed)	CCQ (not dedicated to CKD)

Opting not to dialyse : a practitioner research study to explore patient experience	2009	NA		Noble, H.	WRONG OUTCOME (GI symptoms prevalence not assessed systematically)	CCQ (not dedicated to CKD)
Patient-reported gastrointestinal symptom burden and health-related quality of life following conversion from mycophenolate mofetil to enteric-coated mycophenolate sodium.	2006	Transplantation	81 (9)	Chan, L.	WRONG OUTCOME (GSRS subscales instead of GI symptoms prevalence were reported)	CCQ (not dedicated to CKD)
Reduction of gastrointestinal complications in renal graft recipients after conversion from mycophenolate mofetil to enteric-coated mycophenolate sodium.	2011	Transplantation proceedings	43 (5)	Reinke, P.	WRONG OUTCOME (GSRS subscales instead of GI symptoms prevalence were reported)	CCQ (not dedicated to CKD)
The Maastricht Study: an extensive phenotyping study on determinants of type 2 diabetes, its complications and its comorbidities	2014	European journal of epidemiology	29 (6)	Schram, M.T.	WRONG OUTCOME (GI symptoms prevalence not reported)	CCQ (not dedicated to CKD)
"An evil heritage": interview study of pain and autosomal dominant polycystic kidney disease.	2009	Pain management nursing	10 (3)	Heiwe, S.	WRONG OUTCOME (lower GI symptoms prevalence were not assessed)	CCQ (nephrological)
A brief, patient- and proxy-reported outcome measure in advanced illness: Validity, reliability and responsiveness of the Integrated Palliative care Outcome Scale (IPOS).	2019	Palliative medicine	33 (8)	Murtagh, F.E.M.	WRONG POPULATION (lack of subgroup analysis for CKD patients)	CCQ (nephrological)
A Mixed Methods Study of Symptom Experience in Patients With End-Stage Renal Disease.	2020	Nursing research	70 (1)	Ng, M.S.N.	WRONG POPULATION (dialysis-dependent patients)	CCQ (nephrological)
Arabic translation, adaptation and modification of the dialysis symptom index for chronic kidney disease stages four and five	2015	BMC nephrology	16 (1)	Almutary, H.	WRONG OUTCOME (prevalence not reported)	CCQ (nephrological)
Assessment of palliative need in patients with chronic kidney disease by the new Three Levels of Need Questionnaire (3LNQ) is not exhaustive.	2014	Danish medical journal	61 (4)	Blindbaek, L.	WRONG OUTCOME (lower GI symptoms prevalences were not assessed)	CCQ (nephrological)
Bridging "Office-Based Care" With the "Virtual Practice Care Model": Evolving Care for Chronic Kidney Disease Patients in the COVID-19 Pandemic-And Beyond.	2020	Frontiers in medicine	7	Zhao, B.	WRONG OUTCOME (prevalence of GI symptoms not reported)	CCQ (nephrological)
Changes in symptom burden and physical performance with initiation of dialysis in patients with chronic kidney disease.	2014	Hemodialysis international.	19 (1)	Rivara, M.B.	WRONG OUTCOME (lower GI symptoms prevalences were not assessed)	CCQ (nephrological)
Course of symptoms and health-related quality of life during specialized pre-dialysis care.	2014	PloS one	9 (4)	de Goeij, M.C.M.	WRONG OUTCOME (lower GI symptoms prevalences were not assessed)	CCQ (nephrological)
Developing a self-administered CKD symptom assessment instrument.	2009	Nephrology, dialysis, transplantation	25 (1)	Agarwal, R.	WRONG OUTCOME ("Difficult bowel movements" instead of constipation, "Frequent bowel movements" instead of diarrhea; prevalence not reported)	CCQ (nephrological)

Development and usability testing of an electronic patient-reported outcome measure (ePROM) system for patients with advanced chronic kidney disease.	2018	Computers in biology and medicine	101	Aiyegbusi, O.L.	WRONG OUTCOME (prevalence of GI symptoms was not reported)	CCQ (nephrological)
Differences in illness representations in patients with chronic kidney disease.	2015	Journal of renal care	41 (3)	Pagels, A.A.	WRONG OUTCOME ("changed bowel habits" instead of either constipation or diarrhea)	CCQ (nephrological)
Differences in physical symptoms between those with and without kidney disease: a comparative study across disease stages in a UK population.	2021	BMC nephrology	22 (1)	Wilkinson, T. J.	WRONG OUTCOME (lower GI symptoms prevalences were not assessed)	CCQ (nephrological)
Discussions of the Kidney Disease Trajectory by Elderly Patients and Nephrologists: A Qualitative Study	2012	American journal of kidney diseases	59 (4)	Schell, J.O.	WRONG OUTCOME (lower GI symptoms prevalences were not assessed)	CCQ (nephrological)
Effects of Hemodialysis on the Symptom Burden of Terminally Ill and Nonterminally Ill End-Stage Renal Disease Patients.	2018	Journal of palliative medicine	22 (3)	Wu, Yi L.	WRONG OUTCOME (lower GI symptoms prevalences were not assessed)	CCQ (nephrological)
End-of-Life Experience of Older Adults Dying of End-Stage Renal Disease: A Comparison With Cancer.	2017	Journal of pain and symptom management	54 (6)	Wachterman, M.W.	WRONG OUTCOME (lower GI symptoms prevalences were not assessed)	CCQ (nephrological)
Evaluating symptom burden in kidney transplant recipients: validation of the revised Edmonton Symptom Assessment System for kidney transplant recipients - a single-center, cross-sectional study.	2020	Transplant international	33 (4)	Dano, S.	WRONG OUTCOME (lower GI symptoms prevalences were not assessed)	CCQ (nephrological)
Groningen frailty indicator in older patients with end-stage renal disease.	2015	Renal failure	37 (9)	Meulendijks, F. G.	WRONG OUTCOME (lower GI symptoms prevalences were not assessed)	CCQ (nephrological)
Health Outcome Priorities of Older Adults with Advanced CKD and Concordance with Their Nephrology Providers' Perceptions.	2018	Journal of the American Society of Nephrology	29 (12)	Ramer, S.J.	WRONG OUTCOME (prevalence not reported)	CCQ (nephrological)
High Symptom Burden and Low Functional Status in the Setting of Multimorbidity	2017	Journal of the American Geriatrics Society	65 (10)	Portz, J.	WRONG POPULATION (lack of subgroup analysis for CKD patients)	CCQ (nephrological)
Impact of Depression on Long-Term Outcome After Renal Transplantation: A Prospective Cohort Study	2012	Transplantation	94 (10)	Zelle, D.M.	WRONG OUTCOME (lower GI symptoms prevalences were not assessed)	CCQ (nephrological)
Increasing Nephrologist Awareness of Symptom Burden in Older Hospitalized End-Stage Renal Disease Patients.	2019	American journal of nephrology	51 (1)	Jawed, A.	WRONG OUTCOME (lower GI symptoms prevalence were not assessed)	CCQ (nephrological)
Individual quality of life in chronic kidney disease: influence of age and dialysis modality.	2009	Clinical journal of the American Society of Nephrology	4 (4)	Abdel-Kader, K.	WRONG OUTCOME (prevalence of GI symptoms was not reported)	CCQ (nephrological)
Kidney symptom questionnaire: Development, content validation and relationship with quality of life	2018	Journal of renal care	44 (3)	Brown, S. A.	WRONG OUTCOME (lower GI symptoms prevalences were not assessed)	CCQ (nephrological)
Living with moderate to severe renal failure from the perspective of patients	2016	BMC nephrology	17 (1)	Schipper, K.	WRONG OUTCOME (lower GI symptoms prevalences were not assessed)	CCQ (nephrological)
Pain, sleep disturbance, and quality of life in patients with chronic kidney disease.	2007	Clinical journal of the American Society of Nephrology	2 (5)	Cohen, S.D.	WRONG OUTCOME (lower GI symptoms prevalences were not assessed)	CCQ (nephrological)

Patient and Clinician Perspectives on Electronic Patient-Reported Outcome Measures in the Management of Advanced CKD: A Qualitative Study.	2019	American journal of kidney diseases	74 (2)	Aiyegbusi, O.L.	WRONG OUTCOME (lower GI symptoms prevalences were not assessed)	CCQ (nephrological)
Physical and Psychological Burden of Chronic Kidney Disease among Older Adults	2010	American journal of nephrology	31 (4)	McClellan, W.	WRONG OUTCOME (lower GI symptoms prevalences were not assessed)	CCQ (nephrological)
Prognostic implications of predialysis patients' symptoms in peritoneal dialysis patients.	2021	Renal failure	43 (1)	Wang, F.-Y.	WRONG OUTCOME (symptoms prevalence based on retrospective analysis of medical documentation; not self-reported)	CCQ (nephrological)
Psychometric properties of the Czech Integrated Palliative Outcome Scale: reliability and content validity analysis	2020	BMC palliative care	19 (1)	Vlckova, K.	WRONG POPULATION (no CKD patients)	CCQ (nephrological)
Quality of life with conservative care compared with assisted peritoneal dialysis and haemodialysis.	2018	Clinical kidney journal	12 (2)	Iyasere, O.	WRONG OUTCOME (prevalence of GI symptoms not reported)	CCQ (nephrological)
Rapid Electronic Capturing of Patient-Reported Outcome Measures in Older Adults With End-Stage Renal Disease: A Feasibility Study:	2020	The American journal of hospice & palliative care	38 (5)	Gabbard, J.	WRONG POPULATION (hemodialysis patients)	CCQ (nephrological)
Serious Illness Treatment Preferences for Older Adults with Advanced CKD.	2019	Journal of the American Society of Nephrology	30 (11)	Baddour, N.A.	WRONG OUTCOME (prevalence not reported)	CCQ (nephrological)
Severe fatigue after kidney transplantation: a highly prevalent, disabling and multifactorial symptom	2013	Transplant international	26 (10)	Goedendorp, M.M.	WRONG OUTCOME (lower GI symptoms prevalences were not assessed)	CCQ (nephrological)
Spanish modified version of the palliative care outcome scale-symptoms renal: cross-cultural adaptation and validation	2016	BMC nephrology	17 (1)	Gutiérrez Sánchez, D.	WRONG OUTCOME (prevalence not reported)	CCQ (nephrological)
Symptom burden in patients with chronic kidney disease not requiring renal replacement therapy.	2017	Clinical kidney journal	10 (6)	Brown, S. A.	WRONG OUTCOME (lower GI symptoms prevalence not assessed)	CCQ (nephrological)
Symptom Burden of Adults with Type 2 Diabetes Across the Disease Course: Diabetes & Aging Study	2012	Journal of general internal medicine	27 (12)	Sudore, R. L.	WRONG OUTCOME (registry-type study)	CCQ (nephrological)
Symptom Clusters From Dialysis to Renal Transplantation: A Five-Year Longitudinal Study.	2015	Journal of pain and symptom management	51 (3)	Amro, A.	WRONG OUTCOME (lower GI symptoms prevalences were not assessed)	CCQ (nephrological)
Symptom experience in non-dialysis-dependent chronic kidney disease: A qualitative descriptive study.	2017	Journal of renal care	43 (4)	Pugh-Clarke, K.	WRONG OUTCOME ("Gastrointestinal disturbances" instead of either constipation or diarrhea)	CCQ (nephrological)
The impact of fatigue on daily activity in people with chronic kidney disease.	2010	Journal of clinical nursing	19 (21)	Bonner, A.	WRONG OUTCOME (lower GI symptoms prevalences were not assessed)	CCQ (nephrological)
Towards a symptom cluster model in chronic kidney disease: A structural equation approach.	2017	Journal of advanced nursing	73 (10)	Almutary, H.	WRONG POPULATION (lack of subgroup analysis for non-dialysis CKD patients)	CCQ (nephrological)
Tracking patients with advanced kidney disease in the last 12 months of life	2018	Journal of renal care	44 (2)	Bonner, A.	WRONG POPULATION (lack of subgroup analysis for non-dialysis CKD patients)	CCQ (nephrological)
Trajectories of illness in stage 5 chronic kidney disease: a longitudinal study of patient symptoms and concerns in the last year of life.	2011	Clinical journal of the American Society of Nephrology	6 (7)	Murtagh, F.E.M.	WRONG OUTCOME (prevalence not reported)	CCQ (nephrological)

Understanding the Experience of stress on initiation of Haemodialysis: A Phenomenological Study	2014	International Journal of Nursing	3 (1)	Tarachand, J.S.	WRONG POPULATION (hemodialysis patients)	CCQ (nephrological)
Unmet palliative care needs among patients with end-stage kidney disease: a national registry study about the last week of life	2017	Journal of pain and symptom management	55 (2)	Axelsson, L.	WRONG OUTCOME (lower GI symptoms prevalences were not assessed)	CCQ (nephrological)
Validation of the IPOS-Renal Symptom Survey in Advanced Kidney Disease: A Cross-sectional Study.	2018	Journal of pain and symptom management	56 (2)	Raj, R.	WRONG POPULATION (lack of subgroup analysis for non-dialysis CKD patients)	CCQ (nephrological)
A High Prevalence of Abnormal Nutrition Parameters Found in Predialysis End-Stage Kidney Disease: Is It a Result of Uremia or Poor Eating Habits?	2014	Journal of renal nutrition	24 (5)	Chan, M.F.	WRONG OUTCOME (lower GI symptoms prevalence not assessed)	CCIS
Assessment of palliative need in patients with chronic kidney disease by the new Three Levels of Need Questionnaire (3LNQ) is not exhaustive.	2014	Danish medical journal	61 (4)	Blindbaek, L.	WRONG OUTCOME (lower GI symptoms prevalence not assessed)	CCIS
Assessment of Quality of Life in Dialysis and Non-Dialysis Chronic Kidney Disease Patients	2017	NA		Islam, M.S.	WRONG POPULATION (unclear settings: probably inpatients)	CCIS
Better health-related quality of life in kidney transplant patients compared to chronic kidney disease patients with similar renal function.	2021	PloS one	16 (10)	Ryu, J.	WRONG OUTCOME (lower GI symptoms prevalence was not assessed)	CCIS
Changes in symptom burden and physical performance with initiation of dialysis in patients with chronic kidney disease.	2014	Hemodialysis international.	19 (1)	Rivara, M.B.	WRONG OUTCOME (lower GI symptoms prevalence was not assessed)	CCIS
Chronic Renal Insufficiency Cohort (CRIC) Study: Baseline Characteristics and Associations with Kidney Function	2009	Clinical journal of the American Society of Nephrology	4 (8)	Lash, J.P.	WRONG OUTCOME (GI symptom prevalence was not reported)	CCIS
CKD in Elderly Patients Managed without Dialysis: Survival, Symptoms, and Quality of Life	2015	Clinical journal of the American Society of Nephrology	10 (2)	Brown, M.	WRONG OUTCOME (GI symptom prevalence was not reported)	CCIS
Clinical events and patient-reported outcome measures during CKD progression: findings from the Chronic Renal Insufficiency Cohort Study.	2020	Nephrology, dialysis, transplantation	36 (9)	Grams, M. E.	WRONG OUTCOME (lower GI symptoms prevalence not assessed)	CCIS
Clinical features and CKD-related quality of life in patients with CKD G3a and CKD G3b in China: results from the Chinese Cohort Study of Chronic Kidney Disease (C-STRIDE).	2017	BMC nephrology	18 (1)	Peng, Z.	WRONG OUTCOME (lower GI symptoms prevalence not assessed)	CCIS
Course of symptoms and health-related quality of life during specialized pre-dialysis care.	2014	PloS one	9 (4)	de Goeij, M. C.M.	WRONG OUTCOME (lower GI symptoms prevalence was not assessed)	CCIS
Development of the Chronic Kidney Disease Symptom Index – Sri Lanka; a symptom assessment instrument for Chronic Kidney Disease patients	2017	Journal of the Postgraduate Institute of Medicine	4 (1)	Sameera J.S.	WRONG OUTCOME (GI symptoms prevalence not reported)	CCIS

Differences In Illness Representations In Patients With Chronic Kidney Disease.	2015	Journal of renal care	41 (3)	Pagels, A.A.	WRONG OUTCOME ("changed bowel habits")	CCIS
Dolor músculo-esquelético en pacientes con enfermedad renal crónica	2016	Nefrologia	36 (4)	Caravaca, F.	WRONG OUTCOME (lower GI symptoms prevalence not assessed)	CCIS
Elements of Palliative Care in the Last 6 Months of Life: Frequency, Predictors, and Timing	2019	Journal of general internal medicine	35 (3)	Ernecoff, N.C.	WRONG OUTCOME (appropriate symptom management instead of symptom prevalence was reported)	CCIS
Event-related distress in kidney disease patients	2011	Nephrology, dialysis, transplantation	27 (1)	Ramer, S.J.	WRONG OUTCOME (GI symptom prevalence was not reported)	CCIS
Exploring Symptoms In Patients Managed Without Dialysis: A Qualitative Research Study	2010	Journal of renal care	36 (1)	Noble, H.	WRONG OUTCOME (prevalence of "Bowel and bladder problems" was reported)	CCIS
Gastointestinal-specific patient-reported outcome instruments differentiate between renal transplant patients with or without GI complications	2005	Transplantation proceedings	37 (2)	Kleinman, L.	WRONG OUTCOME (GSRS subscale rather than symptoms were assessed)	CCIS
Health related quality of life in chronic kidney disease; a descriptive study in a rural Sri Lankan community affected by chronic kidney disease	2020	Health and Quality of Life Outcomes	18 (1)	Sameera S.	WRONG OUTCOME (GI symptoms prevalence not reported)	CCIS
Kidney Disease Symptoms before and after Kidney Transplantation.	2021	Clinical journal of the American Society of Nephrology	16 (7)	Taylor, K.	WRONG OUTCOME (lower GI symptoms prevalence not assessed)	CCIS
Palliative Care Consultation in Advanced Chronic Kidney Disease with Pain.	2018	Journal of palliative medicine	21 (6)	Chan, K.Y.	WRONG OUTCOME (lower GI symptoms prevalence not assessed)	CCIS
Physical Symptom Cluster Subgroups in Chronic Kidney Disease.	2019	Nursing research	69 (2)	Lockwood, M.B.	WRONG OUTCOME (lower GI symptoms prevalence not assessed)	CCIS
Quality of Life and Physical Function in Older Patients on Dialysis: A Comparison of Assisted Peritoneal Dialysis with Hemodialysis	2015	Clinical journal of the American Society of Nephrology	11 (3)	Iyasere, O.	WRONG POPULATION (only dialysis-dependent patients)	CCIS
Quality of Life and Survival in Patients with Advanced Kidney Failure Managed Conservatively or by Dialysis	2012	Clinical journal of the American Society of Nephrology	7 (12)	Da Silva-Gane, M.	WRONG OUTCOME (GI symptoms prevalence not assessed)	CCIS
Quality of life in Chronic Kidney Disease (CKD): A cross-sectional analysis in the Renal Research Institute-CKD study	2005	American journal of kidney diseases	45 (4)	Perlman, R.L.	WRONG OUTCOME (GI symptoms not assessed)	CCIS
Quality of Life in Pre-dialysis patients with Chronic Kidney Disease at Glomerular Filtration Rates	2013	Journal of Korean Biological Nursing Science	15 (2)	Kim, H.W.	WRONG OUTCOME (lower GI symptoms prevalence not assessed)	CCIS
Quality of life with conservative care compared with assisted peritoneal dialysis and haemodialysis.	2018	Clinical kidney journal	12 (2)	Iyasere, O.	WRONG OUTCOME (GI symptoms prevalence not reported)	CCIS
Relationships Between Illness Perceptions, Coping and Psychological Morbidity in Kidney Transplants Patients.	2016	The American journal of the medical sciences	351 (3)	Knowles, S.R.	WRONG OUTCOME (GI symptoms prevalence not assessed)	CCIS

Relevance of heat stress and dehydration to chronic kidney disease (CKDu) in Sri Lanka	2019	Preventive medicine reports	15	Jayasekara, K.B.	WRONG POPULATION (lack of subgroup analysis for CKD subgroup)	CCIS
Screening for constipation in palliative care patients.	2009	Journal of palliative medicine	12 (10)	Noguera, A.	WRONG POPULATION (lack of analysis for CKD patients)	CCIS
Self-rated health, quality of life and appetite as predictors of initiation of dialysis and mortality in patients with chronic kidney disease stages 4-5: a prospective cohort study.	2018	BMC research notes	11 (1)	Grove, B.E.	WRONG OUTCOME (lower GI symptoms prevalence not assessed)	CCIS
Sleep disorders, depressive symptoms and health-related quality of life--a cross-sectional comparison between kidney transplant recipients and waitlisted patients on maintenance dialysis	2010	Nephrology, dialysis, transplantation	26 (3)	Kovacs, A.	WRONG OUTCOME (lower GI symptoms prevalence not assessed)	CCIS
Study Of Clinical Profile Of Chronic Kidney Disease In Non-Diabetic Patients	2021	International Journal of Advances in Medicine	8 (8)	Kumar, U R.	WRONG OUTCOME (lower GI symptoms prevalence not assessed)	CCIS
The SF36 as an outcome measure of services for end stage renal failure.	1998	Quality in health care	7 (4)	Wight, J	WRONG OUTCOME (lower GI symptoms prevalence not assessed)	CCIS
The suffering of advanced chronic renal patients and their relationship with symptoms in loja, ecuador	2021	International journal of environmental research and public health	18 (10)	Bonilla-Sierra, P.	WRONG OUTCOME (lower GI symptoms not assessed)	CCIS
The Symptoms Prevalence, Medical Interventions, and Health Care Service Needs for Patients With End-Stage Renal Disease in a Renal Palliative Care Program	2015	The American journal of hospice & palliative care	33 (10)	Kwok, A.O.	WRONG OUTCOME (prevalence of "Bowel problem" and "Distended abdomen" was reported)	CCIS
Trajectory of Quality of Life for Poor Prognosis Stage 5D Chronic Kidney Disease with and without Dialysis	2013	American journal of nephrology	37 (3)	Seow, Y.-Y.	WRONG OUTCOME (GI symptoms prevalence not assessed)	CCIS
Why did I start dialysis? A qualitative study on views and expectations from an elderly cohort of patients with end-stage renal failure starting haemodialysis in the United Kingdom	2011	International urology and nephrology	44 (1)	Stringer, S.	WRONG OUTCOME (lower GI symptoms prevalence not assessed)	CCIS
Wie unterscheiden sich Bedürfnisse und Versorgung in der SAPV in Abhängigkeit von der Grunderkrankung? Auswertungen aus dem Nationalen Hospiz- und Palliativregister	2020	Z Palliativmed	21 (4)	Kaiser, F.	WRONG POPULATION (lack of analysis for CKD patients)	CCIS

*** Abbreviations: DS:** Databases screening; **CCIS:** Citation chasing of included studies; **CCQ:** Citation chasing of questionnaires.

Table S6. Exclusion criteria in the included studies.

First author, reference	Exclusion criteria
Gordon, [21]	Not reported
Yapa, [16]	"Those with medically determined cognitive impairment and/or acute illness (such as peritonitis, myocardial infarction or respiratory infection)"
Ariffin, [22]	"patients less than 18 years of age, with a strong history of non-compliance with medication and treatment, with recent hospitalization (within 3 months) and have evidence of recent active infections (including bacterial and viral)"
Ramos, [17]	"individuals with diabetes mellitus, chronic liver disease, autoimmune disease (i.e., systemic lupus erythematosus, rheumatoid arthritis), congestive heart failure (stages 3/4), human immunodeficiency virus, current malignancy, bowel diseases (i.e., inflammatory bowel diseases, celiac disease), and/or cognitive limitations; who are current smokers; and who are using medications including phosphate binders, immunosuppressants, anti-inflammatories, antibiotics, laxatives, prebiotics, and/or probiotics 3 months preceding the baseline."
Trimingham, [23]	"patients who were in hospital, age <18 years, non-English speaking patients requiring an interpreter, those unable to complete the written or verbal questionnaire (i.e. cognitive impairment) and those who declined to participate"
Sanya, [24]	Diabetic mellitus, coronary heart disease, congestive heart disease, usage of drugs that can influence the cardiovascular or autonomic system
Saini, [25]	"patients aged <18 years and patients who were unclear about their diagnosis and its implications", cancer diagnosis, known reversible kidney disease, renal replacement therapy, eGFR > 16.5
Ohkuma, [26]	"(1) they had drug-induced diabetes or were undergoing steroid treatment; (2) they were being administered renal replacement therapy; (3) they had serious diseases other than diabetes,such as advanced malignancies or decompensated liver cirrhosis; or (4) they were unable to regularly visit a hospital or clinic"; (5) "past history of colon cancer"; (6) "type 1 diabetes"
Ruszkowski, [18,27]	"receiving currently or in the past dialysis; kidney transplantation; cognitive deficits and visual impairment that unable of answering the questionnaire; having a serious illness in an acute treatment phase"
Quintal-Medina, [28]	“sepsis, pericarditis, pleurisy, and uremic encephalopathy”
Meade, [29]	"under 18 years old, from a non-English speaking background requiring an interpreter, were unable to complete the questionnaires or receiving temporary dialysis"
Wizemann, [30]	Not reported
Zhang, [19]	"institutionalized (e.g., prisoner, nursing home or skilled nursing facility resident); unable or unwilling to give consent; unlikely or unable to participate in required study procedures; New York Heart Association class III or IV heart failure (baseline); known cirrhosis; known HIV infection and/or AIDS; pregnant women; previously received dialysis for ≥ 1 mo; previous organ or bone marrow transplant; received immunosuppressive or other immunotherapy for primary renal disease or systemic vasculitis within the past 6 mo; previous chemotherapy or alkylating agents for systemic cancer other than non-melanoma skin cancer within 2 yr; previous diagnosis of multiple myeloma or renal carcinoma; polycystic kidney disease; current participation in interventional clinical trial or in a research study" [31]
Gryp, [20,32]	"age < 18 years, active infection (C-reactive protein > 20 mg/L), active malignancy, cardiovascular event in the past three months, immunosuppressive therapy, inflammatory bowel disease, obesity (BMI > 35 kg/m^2), pregnancy, transplantation, and/or use of non-steroidal anti-inflammatory drugs within the past month"
Miskulin and the HALT-PKD studies investigators, [33,34]	Main exclusion criteria: kidney vascular disease; systemic diseases with kidney involvement; UACR ≥0.5 or 1.0 g/g; diabetes; currently pregnant or intention of becoming pregnant; increased serum potassium level; history of angioneurotic edema, other absolute contraindication for ACEi/ARB or intolerable cough

	associated with ACEi; systemic diseases necessitating NSAIDs, immunosupressant, or immunomodulatory medications; life expectancy <2 yr; "congenital absence of a kidney or history of a total nephrectomy"
Windahl and the EQUAL study investigators, [35–38]	< 65 years, eGFR ≥ 20 mL/min/1.73 m^2, dialysis
Ducharlet, [39]	Patients with eGFR < 15 ml/min/1.73 m^2 were excluded from the analysis
Grove, [15]	“patients reporting change in health and patients who have been in contact with the clinic”
Onodugo, [40]	"severe cardiac disease, cancer, diabetes, collagen and demyelinating diseases, left ventricular systolic dysfunction, or a history of stroke"
Allawi, [41]	Patients who (1) suffer from chronic kidney disease for less than 6 months, (2) are on dialysis, (3) have diseases that might be associated with autonomic neuropathy (diabetes mellitus, heart failure, stroke), (4) use drugs that affect the autonomic nervous system (beta-blockers, tricyclic antidepressants or purgatives), (5) are in the uremic syndrome, i.e. present with persistent nausea & vomiting, encephalopathy or acidotic breathing or bedridden, (5) have GFR > 15 mL/min per 1.73 m^2.
Lee A, [42]	"patients under the care of a nephrologist with an eGFR ≤15 ml/min who had chosen not to dialyse (conservative management); (...) kidney transplant recipients; patients with a colostomy or ileostomy and those with inadequate English language skills to complete a written questionnaire."
Dawson, [14]	Not reported
Abeywickrama, [11]	"Patients with psychiatric/cognitive disorders or language barriers and patients who refused to participate in the study"
Lee SJ, [12]	Not reported
Yong, [43]	"Patients with cognitive impairment or known psychiatric illness"
Senanayake, [13]	"patients with previous renal transplantation, critically ill patients and patients who were unable to provide rational information for any reason (e.g.; mental retardation)" [44]
Abdel-Kader, [45]	"age <18 yr or >90 yr, not residing at home, active malignancy, active infection (pneumonia), active coronary artery disease (e.g., unstable angina, myocardial infarction) within the last 6 mo, advanced cirrhosis, advanced dementia, active alcohol abuse, active treatment for sleep apnea, refractory psychiatric disease, or an unsafe home environment"
Wan Zukiman, [46]	"pregnancy; presence of any type of acute psychiatric disorder that warrant hospitalization, acute medical illnesses, or malignancy; lack of capacity to give informed consent; inability to communicate fluently in Malay or English language; or illiteracy"
Gutiérrez Sánchez, [47–50]	"Patients with cognitive impairment and those under 18 years of age"
Murtagh, [51,52]	"Patients who lacked capacity to consent to research participation (as judged by clinician assessment)"
Turkmen, [53]	„diabetic kidney disease or other kidney disease including glomerulonephritis, lupus nephritis, systemic vasculitis proven by kidney biopsy”, age > 70
Brennan, [54]	Not reported (patients with age < 18 years old, lack of decision for a conservative management of CKD G5 were not included)
Murphy, [55]	Not reported
Taira, [56]	Not reported
Purtell & Sowa, [57,58]	Not reported
De Miguel, [59]	Not reported
Almutary, [60,61]	"cognitive impairment that would preclude voluntary, informed consent, and those with critical conditions"

Table S7. Risk of bias in included studies.

Title [a], reference	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9
Abnormal intestinal bile acid distribution in azotaemic man: a possible role in the pathogenesis of uraemic diarrhea [21]	No	Unclear	No	No	Unclear	Unclear	Unclear	Not applicable	Unclear
Alterations in symptoms and health-related quality of life as kidney function deteriorates: A cross-sectional study [16]	Yes	No	Yes	Unclear	Unclear	Yes	Yes	Not applicable	Yes
Appetite and gastrointestinal symptoms in end stage renal disease patients [22]	Unclear	Unclear	No	No	Unclear	No	Unclear	Not applicable	Unclear
Bowel Habits and the Association With Uremic Toxins in Non-Dialysis-Dependent Chronic Kidney Disease Patients [17]	No	Unclear	No	Yes	Unclear	Yes	Yes	Yes	Unclear
Bowel health in chronic kidney disease: Patient perceptions differ from clinical definitions [23]	Unclear	No	No	No	Unclear	Yes	Yes	Not applicable	Unclear
Cardiovascular autonomic neuropathy in non-diabetic Nigerian patients with chronic renal failure [24]	No	No	No	No	Unclear	Unclear	Yes	No	Unclear
Comparative pilot study of symptoms and quality of life in cancer patients and patients with end stage renal disease [25]	Unclear	Unclear	No	No	Unclear	Yes	Unclear	Not applicable	Unclear
Constipation and diabetic kidney disease: The Fukuoka Diabetes Registry [26]	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Unclear	Unclear
Constipation and the Quality of Life in Conservatively Treated Chronic Kidney Disease Patients: A Cross-sectional Study [18,27]	Yes	Yes	No	Yes	Unclear	Yes	Not applicable	Yes	Yes
Factors associated with residual symptom burden in patients with peritoneal dialysis: a cohort study [28]	No	Unclear	No	Yes	Unclear	Yes	Unclear	Not applicable	Unclear
Gastrointestinal symptom burden and dietary intake in patients with chronic kidney disease [29]	Yes	No	No	Yes	Yes	Yes	Yes	Unclear	Yes

Gastrointestinal symptoms in patients suffering from chronic uremia [30]	Unclear	Unclear	No	No	Unclear	No	Unclear	Not applicable	Unclear
Gastrointestinal symptoms, inflammation and hypoalbuminemia in chronic kidney disease patients: a cross-sectional study [19]	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	Yes	Not applicable	Yes
Gut microbiota generation of protein-bound uremic toxins and related metabolites is not altered at different stages of chronic kidney disease [20,32]	Unclear	Unclear	No	Yes	Unclear	Yes	Yes	No	Unclear
Health-Related Quality of Life in Patients With Autosomal Dominant Polycystic Kidney Disease and CKD Stages 1–4: A Cross-sectional Study [33,34]	No	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes
Patient-Reported Measures and Lifestyle Are Associated With Deterioration in Nutritional Status in CKD Stage 4-5: The EQUAL Cohort Study [35–38]	Unclear	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear
Patient-reported outcome measures and their utility in the management of patients with advanced chronic kidney disease [39]	Unclear	Unclear	No	No	Unclear	Yes	Unclear	Yes	No
Patient-reported outcome measures for clinical decision-making in outpatient follow-up: validity and reliability of a renal disease questionnaire [15]	Unclear	Yes	No	No	Unclear	Yes	Yes	Not applicable	No
Predictors of autonomic dysfunction among pre-dialysis chronic kidney disease patients in Nigeria [40]	No	Unclear	No	No	Unclear	Unclear	Unclear	No	Unclear
Prediction of autonomic neuropathy in chronic kidney disease (stage 5) Iraqi patients (case control study) [41]	No	Unclear	No	No	Unclear	Unclear	Unclear	No	Unclear
Prevalence of constipation in patients with advanced kidney disease [42]	Yes	Yes	No	No	Unclear	No	Yes	Yes	Yes

Prevalence of Taste Changes and Association with Other Nutrition-Related Symptoms in End-Stage Kidney Disease Patients [14]	Unclear	Unclear	No	No	Unclear	Yes	Unclear	Yes	Unclear
Quality of Life and Symptom Burden among Chronic Kidney Disease of Uncertain Etiology (CKDu) Patients in Girandurukotte, Sri Lanka [11]	No	Yes	No	No	Unclear	Yes	Unclear	Not applicable	Unclear
Relationship between symptom clusters and quality of life in patients at stages 2 to 4 chronic kidney disease in Korea [12]	Unclear	Unclear	No	No	Unclear	Yes	Unclear	Yes	Unclear
Symptom burden and quality of life in end-stage renal disease: a study of 179 patients on dialysis and palliative care [43]	Yes	Yes	No	No	Unclear	No	Yes	Not applicable	Unclear
Symptom burden in chronic kidney disease; a population based cross sectional study [13]	Yes	Yes	Yes	No	Unclear	Yes	Yes	Not applicable	Yes
Symptom burden, depression, and quality of life in chronic and end-stage kidney disease [45]	Unclear	Unclear	No	No	Unclear	Yes	Unclear	Unclear	Unclear
Symptom Prevalence and the Negative Emotional States in End-Stage Renal Disease Patients with or without Renal Replacement Therapy: A Cross-Sectional Analysis [46]	Yes	Yes	No	Yes	Yes	Yes	Yes	Not applicable	Yes
Symptomatic profile of patients with Chronic Kidney Disease Stage 4 and 5 [47–50]	Yes	Unclear	No	No	Unclear	Yes	No	Not applicable	Unclear
Symptoms in advanced renal disease: a cross-sectional survey of symptom prevalence in stage 5 chronic kidney disease managed without dialysis [51,52]	Unclear	Yes	No	Yes	Yes	Yes	Unclear	Yes	Yes
The Prevalence of Fabry Disease in Patients with Chronic Kidney Disease in Turkey: The TURKFAB Study [53]	No	Yes	No	No	Not applicable	No	Unclear	Not applicable	Unclear
The symptoms of patients with CKD stage 5 managed without dialysis [54]	Yes	Unclear	No	Yes	Unclear	Yes	Yes	Not applicable	Unclear

Understanding symptoms in patients with advanced chronic kidney disease managed without dialysis: use of a short patient-completed assessment tool [55]	Unclear	Unclear	No	Unclear	Unclear	Yes	Yes	Not applicable	Unclear
Urinary concentrations of neonicotinoid insecticides were related to renal tubular dysfunction and neuropsychological complaints in Dry-zone of Sri Lanka [56]	No	Unclear	No	No	Unclear	Unclear	Yes	Not applicable	Unclear
The Kidney Supportive Care programme: characteristics of patients referred to a new model of care [57,58]	Unclear	Yes	No	No	Yes	Yes	Yes	Not applicable	Not applicable
What are the last months of life like for advanced chronic renal failure patients who are not considered candidates for treatment with haemodialysis or peritoneal dialysis [59]	Yes	Yes	No	Yes	Yes	Unclear	Unclear	Not applicable	Not applicable
Which patients with chronic kidney disease have the greatest symptom burden? A comparative study of advanced CKD stage and dialysis modality [60]	Yes	No	No	Unclear	Unclear	Yes	Yes	Not applicable	Unclear

[a] If a study had more than one report, the title of the oldest one or most important article has been chosen.

Questions according to Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Prevalence Studies [62]. Q1: Was the sample frame appropriate to address the target population? Q2: Were study participants sampled in an appropriate way? Q3: Was the sample size adequate? Q4: Were the study subjects and the setting described in detail? Q5: Was the data analysis conducted with sufficient coverage of the identified sample? Q6: Were valid methods used for the identification of the condition? Q7: Was the condition measured in a standard, reliable way for all participants? Q8: Was there appropriate statistical analysis? Q9: Was the response rate adequate, and if not, was the low response rate managed appropriately?

Table S8. Severity of self-reported constipation

	Total (N analyzed participants)	Mild (Slight)	Moderate	Severe	Overwhelming (very severe)
CKD G1-2					
Lee SJ (G1-2)	7	4	2	1	0
Prevalence (95% CI) [a]		57.14% (28.6-91.5)	28.57% (0-62.9)	14.29% (0-48.6)	0% (0-34.3)
CKD G3					
Dawson (G3)	1	1	0	0	0
Lee SJ (G3)	36	14	11	6	5
Yapa (G3)	71	19	42	10	0
Prevalence (95% CI) [b]		37.60% (10.4-69.1)	40.92% (12.8-72.2)	15.84% (0-41.2)	5.65% (0-23.9)
CKD G4-5					
Lee SJ (G4-5)	22	9	8	3	2
Dawson (G4-5)	28	15	8	5	0
Murphy	23	9	11	3	0
Sowa	26	16	7	2	1
Yapa (G4-5)	190	73	95	22	0
Sánchez	22	8	7	6	1
Brennan	18	11	3	3	1
Quintal-Medina	31	7	8	12	4
Wan Zukiman	32	26		6	
Ducharlet	15	10		5	
Prevalence (95% CI) [c]		43.81% (32.8-54.4)	34.43% (24.2-44.9)	18.16% (10.3-27.2)	3.60% (0.4-9.0)

[a] Only one study provided data, thus meta-analysis could not be performed. Confidence intervals for multinomial proportions were calculated according to the method of Sison and Glaz. [b] Meta-analysis was conducted using a random-effects model with Freeman–Tukey double arcsine transformation of proportions ($\tau = 0.182$; $I^2 = 82\%$). [c] Data from both Wan Zukiman *et al*. and Ducharlet *et al*. was excluded from the meta-analysis because of the non-comparable format of that data. Meta-analysis of the remaining studies was conducted using random-effects model with Freeman–Tukey double arcsine transformation of proportions ($\tau = 0.064$; $I^2 = 70\%$).

Table S9. Subgroup analysis for self-reported constipation prevalence in chronic kidney disease (CKD) G4-5

Subgroup	N	Prevalence		τ^2	*P* value
		[%]	95% CI		
WHO Region					0.02
Western Pacific	9	41.36	32.94–50.32	0.21	
European	8	31.44	26.78–36.50	0.05	
American	2	38.85	31.55–46.69	0	
Eastern Mediterranean	2	94.60	0.61–100.0	22.48	
South-East Asian	1	42.89	38.35–47.55	-	
Study period					0.05
After 2010	15	43.71	32.26–55.88	0.83	
2000–2010	6	32.59	27.11–38.59	0.03	
Before 2000	1	15.00	4.92–37.58	-	
Average age [a]					0.49
Lower tercile (< 64 y)	7	51.17	24.90–76.81	2.20	
Medium tercile	6	39.12	32.48–46.18	0.03	
Upper tercile (> 75 y)	7	35.40	28.49–42.97	0.12	
Sex [b]					0.58
More males	12	39.00	25.64–54.25	1.08	
More females	8	43.74	36.52–51.24	0.09	

[a] Two studies (Wizemann *et al*. [30] and Ariffin *et al*. [22]) were excluded from the analysis because they did not provide data on the age of participants. Also, average age was not a significant predictor of the prevalence in the meta-regression model ($P = 0.38$).

[b] Two studies (Wizemann *et al*. [30] and Ariffin *et al*. [22]) were excluded from the analysis because they did not provide data on the number of males in CKD G4-5 groups. Also, the percentage of males was not a significant predictor of the prevalence in the meta-regression model ($P = 0.46$).

Table S10. Severity of self-reported constipation (alternative version)

	Total (N analyzed participants)	Not at all	A little (a little bit)	Somewhat	Quite a bit	Very much
CKD G3						
Grove	141	111	21	-	8	1
Prevalence (95% CI) [a]		78.7% (73.0-85.7)	14.9% (9.2-21.9)		5.7% (0-12.7)	0.7% (0-7.7)
CKD G4-5						
EQUAL study	361	22	144	105	70	20
Murtagh	64	41	8	10	5	
Grove	90	62	23	-	5	0
Prevalence (95% CI) [b]		32.5% (0-100)	26.9% (0-100)	23.7% (0-100)	16.9% (0-100)	

[a] Only one study provided data, thus meta-analysis could not be performed. Confidence intervals for multinomial proportions were calculated according to the method of Sison and Glaz. [b] Data from both Grove *et al*. were excluded from the meta-analysis because of the non-comparable format of data (lack of "somewhat" category). Meta-analysis of the remaining studies was conducted using a random-effects model with Freeman–Tukey double arcsine transformation of proportions ($\tau = 0.899$; $I^2 = 99\%$).

Table S11. Relationships between self-reported constipation and health-related quality of life (HRQoL), clinical data, or laboratory tests results

Author, reference (outcome*)	HRQoL	Clinical data	Laboratory data
Lee SJ [12] (P)	Principal component analysis (varimax rotation) revealed that both constipation and diarrhea clustered together with the 'difficulty sleeping' item into the "neurological and bowel problem" symptom cluster. The score of this cluster correlated negatively with summary metrics of health-related quality of life scale SF36v2, i.e. with both physical (r = −0.29 *P*<0.001) and mental (r = −0.31 *P*<0.001) component summaries.	Patients with cardiovascular diseases had a higher score (more severe) of the "neurological and bowel problem" factor (*P* = 0.03), i.e. diarrhea, constipation, and difficulty sleeping. "There were no relationships between the severity of the symptom clusters and gender, age, educational background, having spouses, or current occupations" (*P* values not reported).	There were no significant correlations between score of "neurological and bowel problem" symptom cluster and serum creatinine level (r = 0.05), eGFR (r = −0.11), blood urea nitrogen level (r = −0.08), or hemoglobin level (r = −0.07) (*P* values not reported).
EQUAL study investigators [35–38] (P, S)	Presence of constipation was associated with lower HRQoL measured with the RAND-36: both physical (coefficient: −7.5; SE 1.57; N = 994; *P* <0.001) and mental (coefficient: −8.0; SE 1.49; N = 1086; *P* <0.001) component score. Similarly, constipation severity correlated with both physical (r = −0.19, N = 1001, *P* < 0.001) and mental (r = −0.20, N = 1092, *P* < 0.001) component score. [Information received from the Authors]	There were no differences in age-adjusted prevalence of constipation between women and men of ≥65 years of age (*P* = 0.27). Constipation was one of the symptoms whose prevalence increased the most over the 1-year follow-up period (ca. +8.6%). In the multivariable models, constipation was associated with a decline in nutritional status evaluated with the Subjective Global Assessment tool (SGA; "at least 1 point decline in SGA at any visit during the first 12 months of follow-up"; OR 1.41, 95% CI 1.20-1.67).	NR

Yapa [16] (P, S)	Constipation severity did significantly correlate with summary measures of SF-36v2 questionnaire: both Physical (PCS; r=0.17 (*P* < 0.001) and Mental (MCS; r=0.15, *P* < 0.001) Component Summary. [Information from correspondence with authors]	Prevalence of constipation was significantly associated with the stage of CKD (*P* < 0.05); the increasing trend was observed from G3b stage (31.7%) through G4 (39.6%) up to G5 stage (46.2%). Otherwise, severity was not significantly associated with stage of CKD (*P* value not reported). Patients with CKD G5 did not significantly differ from dialysis patients in the case of constipation prevalence (46% vs G5D: 43%; *P* = 0.50).	NR
Dawson [14] (P)	In the conservatively managed patients, there was a significant association between taste disturbances and constipation prevalence (*P* = 0.005).	NR	NR
Sanya [24] (P)	NR	CKD patients with autonomic neuropathy reported constipation more frequently than CKD patients without autonomic neuropathy (59% vs 33%).	NR
Onodugo [40] (P)	NR	In the multivariable regression model, constipation was not associated with autonomic dysfunction (*P* = 0.39).	NR
Ducharlet [39] (P)	NR	Patients with CKD G4 did not differ from dialysis patients in the case of constipation prevalence (48% vs 56%; *P* = 0.45).	NR
Abdel-Kader [45] (P, S)	NR	Neither median severity of constipation (*P* = 0.7) nor prevalence of constipation (G4-5: 33% vs G5D: 26%, *P* = 0.3) differed between non-dialysis and dialysis patients.	NR
Ariffin [22] (P)	NR	Non-dialysis patients with CKD G5 did not significantly differ in the self-reported constipation prevalence from healthy controls (22% vs 13%, *P* = 0.16) or dialysis-dependent patients (22% vs 30%, *P* = 0.27).	NR
Lee A [42] (P)	NR	Non-dialysis patients with CKD G5 did not significantly differ in the self-reported constipation prevalence from dialysis-dependent patients (62% vs G5D: 42%, *P* = 0.09).	NR
Yong [43] (P)	NR	Non-dialysis patients with CKD G5 did not significantly differ in the self-reported constipation prevalence from dialysis-dependent patients (36% vs G5D: 28%, *P* = 0.31).	NR
Wan Zukiman [46] (P)	NR	Non-dialysis patients with CKD G5 did not significantly differ in the self-reported constipation prevalence from dialysis-dependent patients (32% vs G5D: 21%, *P* = 0.08).	NR
Taira [56] (P)	NR	Non-dialysis patients with CKD of unknown etiology (eGFR not reported) had higher prevalence of self-reported constipation than their healthy family members and neighbors (13.3% vs 1.3%, *P* = 0.019).	NR
Gutiérrez Sánchez [47,49] (P, S)	NR	Factor analysis (maximum likelihood extraction, oblimin rotation; both non-dialysis and dialysis-dependent CKD G5), constipation is not clustered together with other gastrointestinal (diarrhea, nausea, vomiting) or "neuropsychological" (weakness, mouth problems, poor mobility, difficulty sleeping, feeling anxious, and feeling depressed)	NR

		symptoms. Non-dialysis patients with CKD G4-5 had higher prevalence of self-reported constipation than dialysis-dependent patients (41% vs G5D: 25%, *P* = 0.015).	
Almutary [61] (P, S)	NR	Factor analysis (principal axis factoring, oblique rotation; CKD patients including dialysis-dependent) revealed that gastrointestinal symptom cluster includes nausea and vomiting as core symptoms across all dimensions. Constipation is not related to this cluster at any dimension. Non-dialysis patients with CKD G5 had lower prevalence of self-reported constipation than dialysis-dependent patients (23.7% vs G5D: 45%, *P* = 0.012).	NR
Murtagh [51,52] (P)	NR	In the subgroup of patients who died, the prevalence of constipation within a month before death was 1.87 times higher than in the whole baseline group (65% [95% CI: 50-78%]).	NR

* Outcome that was tested for association with other data. NR: not reported; P: prevalence; S: severity.

Table S12. Relationships between functional constipation and HRQoL, clinical data, or laboratory tests results.

Authors	HRQoL	Laboratory data	Clinical data
Ruszkowski, [18,27]	Functional constipation (FC) was significantly associated with worse assessment of some domains of HRQoL: role limitations due to physical health problems, bodily pain, and vitality. CKD patients with FC were more likely to have impaired sleep quality in comparison to patients without FC (PR 2.71, 95% CI 1.21-6.07, *P* = 0.02). The associations maintain to be significant after adjustment for key clinical data. Specifically, FC was significantly associated with severity of insomnia, but not with excessive daytime sleepiness.	When all patients were divided into 3 groups based of eGFR value (≤ 32, 33-43, ≥44 ml/min/1.73 m²), patients with the lowest eGFR had more frequently FC than these with the highest eGFR (adjusted PR 2.85, 95% CI 1.12 to 7.28).	CKD patients who were treated with paracetamol were more likely to have FC than patients not receiving this drug (adjusted PR 2.67, 95% CI 1.07-6.64). Likewise, taking non-steroidal anti-inflammatory drugs was independently associated with lower PR of FC (adjusted PR 0.34, 95% CI 0.11 to 1.00). Gender, age, body mass index were not significantly associated with altered prevalence of FC.
Ramos, [17]	NR	Authors noticed that "using the Rome III criteria, a trend for higher levels of *p*-cresyl sulfate was observed in constipated participants when compared with non-constipated participants"; however, there were no significant associations (*P* values ranged from 0.06 to 0.16).	"No differences were found in gender, age, body mass index, and dietary parameters between constipated and non-constipated groups assessed by both Rome III criteria" (*P* values not reported).
Lee A [42] (P)	NR	NR	Non-dialysis patients with CKD G5 did not significantly differ in the FC prevalence from dialysis-dependent patients (5% vs 13%, *P* = 0.26).

NR: not reported

Table S13. Severity of self-reported diarrhea

	Total (N analyzed participants)	Mild (including very mild, slight)	Moderate	Severe	Overwhelming (very severe)
CKD G1-2					
Lee SJ (G1-2)	6	4	1	0	1
Senanayake (G1-2)	9	3	2	2	2
Prevalence (95% CI) [a]		46.8% (15.5-80.9)	20.0% (0-53.9)	13.2% (0-40.2)	20.0% (0-53.9)
CKD G3					
Abeywickrama (G3)	9	8	1	0	0
Dawson (G3)	1	0	0	1	0
Lee SJ (G3)	12	8	2	1	1
Senanayake (G3)	11	8	2	1	0
Yapa (G3)	19	9	10	0	0
Prevalence (95% CI) [b]		63.0% (43.7-82.4)	25.2% (9.8-45.4)	8.0% (0-20.9)	3.8% (0-13.6)
CKD G4-5					
Abeywickrama (G4-5)	17	15	2	0	0
Brennan	9	3	4	1	1
Dawson (G4-5)	15	7	5	3	0
Lee SJ (G4-5)	5	3	2	0	0
Murphy	6	5	1	0	0
Sowa	15	5	5	5	0
Yapa (G4-5)	66	28	35	3	0
Senanayake (G4-5)	37	10	19	4	4
Sánchez	9	4	4	1	0
Quintal-Medina	26	7	4	11	4
Wan Zukiman	20	18		2	
Ducharlet	13	12		1	
Prevalence (95% CI) [c]		47.1% (33.3-59.7)	35.6% (23.0-48.2)	13.5% (5.4-23.6)	3.9% (0.1-10.9)

[a] Meta-analysis was conducted using a random-effects model with Freeman–Tukey double arcsine transformation of proportions ($\tau = 0.085$; $I^2 = 40\%$). [b] Meta-analysis was conducted using a random-effects model with Freeman–Tukey double arcsine transformation of proportions ($\tau = 0.096$; $I^2 = 49\%$). [c] Data from both Wan Zukiman *et al*. and Ducharlet *et al*. was excluded from the meta-analysis because of the non-comparable format of data. Meta-analysis of the remaining studies was conducted using a random-effects model with Freeman–Tukey double arcsine transformation of proportions ($\tau = 0.111$; $I^2 = 68\%$).

Table S14. Subgroup analysis for self-reported diarrhea prevalence in CKD G4-5

Subgroup	N	Prevalence		τ^2	*P* value
		[%]	95% CI		
WHO Region					< 0.001
Western Pacific	7	20.42	13.97–28.85	0.25	
European	7	18.20	11.13–28.35	0.44	
South-East Asian	3	11.79	5.40–23.83	0.52	
American	2	30.64	23.11–39.38	0.02	
Eastern Mediterranean	1	6.54	3.15–13.09	-	
Study period					0.63
After 2010	15	18.54	13.18–25.43	0.55	
2000–2010	4	16.35	8.88–28.17	0.32	
Before 2000	1	10.00	2.51–32.38	-	
Average age [a]					0.28
Lower tercile (< 62 y)	6	14.86	8.02–25.88	0.69	
Medium tercile	6	25.51	16.74–36.85	0.31	
Upper tercile (> 75 y)	6	18.40	12.39–26.45	0.23	
Sex [b]					0.52
More males	12	20.09	13.54–28.75	0.61	
More females	6	0.1675	11.07–24.54	0.21	

[a] Two studies (Wizemann *et al*. [30] and Ariffin *et al*. [22]) were excluded from the analysis because they did not provide data on the age of participants. Also, average age was not a significant predictor of the prevalence in the meta-regression model ($P = 0.76$).

[b] Two studies (Wizemann *et al*. [30] and Ariffin *et al*. [22]) were excluded from the analysis because they did not provide data on the number of males in CKD G4-5 groups. Also, the percentage of males was not a significant predictor of the prevalence in the meta-regression model ($P = 0.45$).

Table S15. Relationships between self-reported diarrhea and HRQoL, clinical data, or laboratory test results

Authors, reference (outcome*)	HRQoL	Clinical data	Laboratory data
Lee SJ [12] (P, S)	Principal component analysis (varimax rotation) revealed that both constipation and diarrhea clustered together with the 'difficulty sleeping' item into the "neurological and bowel problem" symptom cluster. The score of this cluster correlated negatively with summary metrics of health-related quality of life scale SF36v2, i.e. with both physical (r = −0.289, *P* < 0.001) and mental (r = −0.308, *P* < 0.001) component summaries.	Patients with cardiovascular diseases had a higher score (more severe) of the "neurological and bowel problem" factor (*P* = 0.026), i.e. diarrhea, constipation, and difficulty sleeping. "There were no relationships between the severity of the symptom clusters and gender, age, educational background, having spouses, or current occupations" (*P* values not reported).	There were no significant correlations between score of "neurological and bowel problem" symptom cluster and serum creatinine level (r = 0.051), eGFR (r = −0.109), blood urea nitrogen level (r = −0.079), or hemoglobin level (r = −0.069) (*P* values not reported).
EQUAL study investigators [35–38] (P, S)	Presence of diarrhea was associated with lower HRQoL measured with the RAND-36: both physical (coefficient: −6.6; SE 1.63; N = 996; *P* <.0001) and mental component score (coefficient: −9.2; SE 1.54; N = 1084; *P* <.0001). Also, the severity of diarrhea correlated negatively with both physical (Pearson r = −0.16; N = 998; *P* <.0001) and mental component score (Pearson r = −0.20; N = 1089; *P* <.0001) [Information received from the Authors].	The age-adjusted prevalence of diarrhea was higher in women than in men of ≥65 years of age (*P* = 0.007). Diarrhea was not significantly associated with a decline in nutritional status evaluated with the Subjective Global Assessment tool (SGA; "at least 1 point decline in SGA at any visit during the first 12 months of follow-up"). The prevalence of diarrhea decreased over the 1-year follow-up period (about −2.4%).	NR
Yapa [16] (P, S)	Diarrhea severity did not significantly correlate with summary measures of SF-36v2 questionnaire: Physical (PCS; r=0.001, *P* = 0.97) nor Mental (MCS; r=0.030, *P* = 0.38) Component Summary. [Information from correspondence with authors].	Both prevalence (*P* < 0.05) and severity (*P* < 0.001) of diarrhea were significantly associated with the stage of CKD. Patients with CKD G3b, G4, and G5 had significantly lower severity of diarrhea than dialysis patients (all *P* < 0.001). Patients with CKD G5 have more severe diarrhea than patients with G3b (*P* < 0.05).	NR
Dawson [14] (P)	In the conservatively managed patients, there was not a significant association between taste disturbances and diarrhea prevalence (*P* = 0.18).	NR	NR
Almutary [61] (P, S)	NR	Factor analysis (principal axis factoring, oblique rotation, CKD patients including dialysis-dependent) revealed that gastrointestinal symptom cluster includes nausea and vomiting as core symptoms across all dimensions. Diarrhea is related to this cluster in distress and severity dimensions only. Non-dialysis patients with CKD G5 had lower prevalence of self-reported diarrhea than dialysis-dependent patients (2.6% vs G5D: 28.6%, *P* < 0.001).	NR
Gutiérrez Sánchez [47,49] (P, S)	NR	Factor analysis (maximum likelihood extraction, oblimin rotation; both non-dialysis and dialysis-dependent CKD G5), diarrhea is clustered together with nausea and vomiting.	NR

		Non-dialysis patients with CKD G4-5 did not significantly differ in the self-reported diarrhea prevalence from dialysis-dependent patients (13.7% vs G5D: 17.9%, *P* = 0.47).	
Sanya [24] (P)	NR	There was not significant association between reporting diarrhea and having autonomic neuropathy in CKD patients.	NR
Onodugo [40] (P)	NR	In the multivariable regression model, autonomic dysfunction was not associated with diarrhea (*P* = 0.11), but was associated with nocturnal diarrhea (Odds ratio = 29; *P* = 0.02).	NR
Abdel-Kader [45]	NR	Median severity of diarrhea was lower in non-dialysis patients than in dialysis patients (*P* = 0.04), but there was no difference in the prevalence of it between these groups (G4-5: 25% vs G5D: 28%, *P* = 0.7).	NR
Senanayake [13] (P)	NR	Non-dialysis patients with CKD G5 had lower prevalence of self-reported diarrhea than dialysis-dependent patients (4% vs G5D: 16%, *P* = 0.016).	NR
Ducharlet [39] (P)	NR	Patients with CKD G4 had lower prevalence of diarrhea in comparison to dialysis patients (42% vs 64%; *P* = 0.03).	NR
Wan Zukiman [46] (P)	NR	Non-dialysis patients with CKD G5 did not significantly differ in the self-reported diarrhea prevalence from dialysis-dependent patients (20% vs G5D: 10%, *P* = 0.11).	NR
Ariffin [22] (P)	NR	Non-dialysis patients with CKD G5 did not significantly differ in the self-reported diarrhea prevalence from healthy controls (8% vs 4%, *P* = 0.30) or dialysis-dependent patients (8% vs 8.3%, *P* = 0.94).	NR
Taira [56] (P)	NR	Non-dialysis patients with CKD of unknown etiology (eGFR not reported) G5 did not significantly differ in the self-reported diarrhea prevalence from their healthy family members and neighbors (13.3% vs 2.6%, *P* = 0.07).	NR
Murtagh [51,52] (P)	NR	In the subgroup of patients who died, the prevalence of diarrhea within a month before death was nearly the same as in the whole baseline group [8% (95% CI: 2 to 20%)].	NR
Gordon [21] (P)	NR	NR	The composition of bile acids in the proximal small intestine after the test meal in CKD patients with diarrhea differs from the composition observed in healthy patients. Three patients with severe diarrhea had a decreased percentage of deoxycholic acid (DCA; mean 7.5%) and elevated percent of ursodeoxycholic acid (UDCA; mean 14.5%).

			Patient with severe uremia but without diarrhea had a more normal composition of bile acids (DCA: 23.7% [norms: 28±11]; UDCA: 2.4% [norms: <1]). Authors concluded: "Patients with low DCA and UDCA acid greater than 3% of total bile acids have symptoms of watery diarrhea. In this patient population, it appears that both of these bile acid abnormalities must be present for the symptom complex of diarrhea to occur".

* Outcome that was tested for association with other data. NR: not reported; P: prevalence; S: severity.

Table S16. Severity of abdominal bloating

	Total (N analyzed participants)	Mild ("A little"*)	Moderate („Somewhat"*)	Severe („Quite a lot"*)	Very severe ("very much"*)
CKD G1-2					
Ruszkowski	10	8	2	0	0
Prevalence (95% CI) [a]		80% (70-100)	20% (10.0-48.7)	0% (0-28.7)	0% (0-28.7)
CKD G3					
Ruszkowski	30	15	14	1	0
Prevalence (95% CI) [a]					
CKD G4-5					
Ruszkowski (%, [95% CI]) [a]	16	8 [50.0% (31.3-78.0)]	5 [31.25% (12.5-59.2)]	2 [12.5% (0-40.5)]	1 [6.25% (0-34.2)]
Murtagh (%, [95% CI]) [b]	14	12 [85.7% (57.2-98.2)]		2 [14.3% (1.8-42.8)]	
Yong	10	Mean (SD) 3.5 (1.7) in scale 0-10			

* We put answers from Murtagh *et al*. in brackets. [a] Confidence intervals for multinomial proportions were calculated according to the method of Sison and Glaz. [b] Confidence intervals for binomial proportions were calculated according to the conservative exact Clopper–Pearson method.

Table S17. Relationships between self-reported abdominal bloating and HRQoL, clinical data, or laboratory test results.

Author	HRQoL	Laboratory data	Clinical data
Ruszkowski [18,27]	Presence of bloating was associated with worse assessment of bodily pain, vitality, and mental health (SF36v2 domains).	There was no significant relationship between eGFR and either prevalence or severity of abdominal bloating.	NR
Meade [29]	NR	NR	In the combined group of non-dialysis and dialysis CKD patients, "there was no significant association of fruit, vegetables, wholegrains or legumes intake with any GI symptom" (*P* not reported).
Murtagh [51,52]	NR	NR	In the subgroup of patients who died, the prevalence of bloating within a month before death was 1.64 times higher than in the whole baseline group (35% [95% CI: 22-50%]).
Ariffin [22] (P)	NR	NR	Non-dialysis patients with CKD G5 did not significantly differ in the self-reported bloating prevalence from healthy controls (16% vs 10%, *P* = 0.29) or dialysis-dependent patients (16% vs 20.5%, *P* = 0.48).
Yong [43] (P, S)	NR	NR	Non-dialysis patients with CKD G5 did not significantly differ in the self-reported bloating prevalence from dialysis-dependent patients (22% vs G5D: 28%, *P* = 0.48). However, non-dialysis patients with CKD G5 had significantly less severe bloating than dialysis-dependent patients reporting this symptom (*P* = 0.04).

Table S18. Abdominal pain prevalence and severity in autosomal dominant polycystic kidney disease.

	Abdominal pain frequency				Abdominal pain intensity		
	Total (N analyzed participants)	never/rarely	sometimes	often/usually/always	N analyzed participants*	median (interquartile range) in males	median (interquartile range) in females
CKD G1-2							
Miskulin	575	420	92	63	97+175	2.0 (1.0–3.0)	2.0(1.0–3.0)
Prevalence (95% CI) [a]		73.0% (69.6-76.7)	16.0% (12.5-19.6)	11.0% (7.5-14.59)		-	-
Prevalence (95% CI) [b]			27.0% (23.4-30.8)			-	-
CKD G3a							
Miskulin	216	155	35	26	39+56	1.0 (1.0–3.0)	2.0 (1.0–4.0)
Prevalence (95% CI) [a]		71.8% (66.2-77.9)	16.2% (10.6-22.3)	12.0% (6.5-18.1)		-	-
Prevalence (95% CI) [b]			28.2% (22.3-34.7)			-	-
CKD G3b-G4							
Miskulin	204	141	33	30	47+66	2.0 (1.0–3.0)	2.0 (1.0–4.0)
Prevalence (95% CI) [a]		69.1% (63.2-75.6)	16.2% (10.3-22.7)	14.7% (8.8-21.2)		-	-
Prevalence (95% CI) [b]			30.9% (24.6-37.7)			-	-

* Number of males and females was shown. [a] Confidence intervals for multinomial proportions were calculated according to the method of Sison and Glaz. [b] Confidence intervals for binomial proportions were calculated according to the conservative exact Clopper–Pearson method.

Table S19. Relationships between self-reported abdominal pain and HRQoL, clinical data, or laboratory tests results.

Author, reference (outcome*)	HRQoL	Clinical data	Laboratory data
Ruszkowski [18,27] (P, S)	Presence of pain in the abdomen was associated with worse assessment of nearly all SF-36v2 HRQoL domains, with exception for role limitations due to emotional problems (RE, P > 0.05) and general health (GH, not assessed in the cited study). Patients reporting abdominal pain more frequently had impaired sleep quality in comparison to those without the symptom (PR 5.33; 95% CI 2.22- 12.79; P < 0.001). The higher severity of abdominal pain, the higher prevalence ratio of impaired sleep quality in comparison to patients without the symptom: mild pain is associated with PR 4.24 (95% CI 1.56-11.52) and at least moderate pain with PR 7.20 (95% CI 2.87-18.03). After adjustment for key clinical data, the associations remained significant (mild: PR 2.91, 95% CI 1.19-7.15; at least moderate: PR 11.04, 95% CI 4.82-25.26).	NR	NR
Miskulin & Nowak, [33,34] (P, S)	NR	"Among patients with eGFR >60 mL/min/1.73 m2, htTKV was not related to the frequency or intensity of abdominal pain in females or males". In contrast to back/radicular pain, there was no significant difference in odds of abdominal pain according to BMI category [normal, overweight, obese). Change in weight during the study was not associated with the significant change in abdominal pain.	"The intensity of (...) abdominal pain on average or at their worst (data not shown) was also not associated with eGFR"
Ariffin [22] (P)	NR	Non-dialysis patients with CKD G5 did not significantly differ in the self-reported abdominal pain prevalence from healthy controls (12% vs 13%, *P* = 0.86) or dialysis-dependent patients (12% vs 16.7%, *P* = 0.43).	NR

* Outcome that was tested for association with other data. NR: not reported; P: prevalence; S: severity.

Table S20. Relationships between stool consistency and HRQoL, clinical data, or laboratory tests results.

Author, reference	HRQoL	Laboratory data	Clinical data
Ruszkowski, [18,27]	Reporting types 1-2 of stool consistency was associated with neither worse HRQoL (any domain) nor altered sleep quality.	Prevalence of type 1-2 consistency was not significantly different between eGFR terciles (*P* values between 0.25 and 0.59).	Besides female sex and increasing age, taking diuretics was independently associated with increased prevalence of reporting type 1-2 stool form (adjusted PR 2.86, 95% CI 1.28-6.37, *P* = 0.01).
Ramos, [17]	NR	Patients with BSS<3 had significantly higher levels of all fractions (serum total, serum free, urinary) of *p*-cresyl sulfate (PCS) in comparison to patients with BSS ≥ 3. "In the multivariate analysis, the association of BSS<3 with PCS was maintained after adjustments for eGFR and protein-fiber ratio".	"No differences were found in gender, age, body mass index, and dietary parameters between constipated and non-constipated groups assessed by (…) BSS" (*P* value not reported).
Gryp, [20,32]	NR	"Fecal dry weight percentage significantly correlated with Bristol stool scale ($P < 0.001$, rs = –0.579)". There were significant negative correlations between BSS and plasma hippuric acid in the total CKD cohort (rs = −0.343, $P < 0.001$) and in stages G1–2 (rs = 0.366, $P = 0.036$); and between BSS and *p*-cresyl sulfate in the total CKD cohort (rs = −0.287, $P = 0.003$) and stages G4–5 (rs = 0.443, $P = 0.012$). Moreover, BSS correlated with the Bray-Curtis-based variation of the microbial composition of stool microbiome.	NR
Meade, [29]	NR	NR	In the combined group of non-dialysis and dialysis CKD patients, "there was no significant association of fruit, vegetables, wholegrains or legumes intake with (...) stool consistency" (*P* value not reported).

BSS: Bristol stool scale

Table S21. Number of bowel movements per week in patients with CKD or diabetic kidney disease.

	Total (N analyzed)	BM < 3	3 <= BM < 7	BM = 7	BM > 7
CKD G1-2					
Ruszkowski [18,27]	16	2	4	5	5
Prevalence (95% CI) [a]		12.5% (0-41.3)	25.0% (6.3-53.8)	31.25% (12.5-60.1)	31.25% (12.5-60.1)
CKD G3					
Ruszkowski [18,27]	67	5	17	34	11
Prevalence (95% CI) [a]		7.5% (0-20.8)	25.4% (14.9- 38.8)	50.7% (40.3-64.1)	16.4% (6.0-29.8)
CKD G4-5					
Meade [29]	134	2	20	63	49
Ruszkowski [18,27]	23	0	10	7	6
Prevalence (95% CI) [b]		1.5% (0-14.7)	26.1% (1.8-58.5)	40.5% (9.4-72.4)	31.9% (4.4-64.4)
CKD eGFR undetermined					
Trimingham [23]	99	0	11	52	36
Prevalence (95% CI) [a]		0% (0-10.9)	11.1% (2-22.1)	52.5% (43.4-63.5)	36.4% (27.3-47.3)
DKD					
Ohkuma (DKD A2-3) [26]	1880	176	571	1133	
Prevalence (95% CI) [a]		9.4% (7.1-11.7)	30.4% (28.1- 32.7)	60.3% (58.0-62.6)	
Ohkuma (DKD G3-5) [26]	1012	96	333	583	
Prevalence (95% CI) [a]		9.5% (6.3-12.7)	32.9% (29.7-36.1)	57.6% (54.4-60.8)	

BM: bowel movements per week; DKD: diabetic kidney disease. [a] Only one study provided data, thus meta-analysis could not be performed. Confidence intervals for multinomial proportions were calculated according to the method of Sison and Glaz. [b] Meta-analysis was conducted using a random-effects model with Freeman–Tukey double arcsine transformation of proportions (I^2 = 88%).

Table S22. Relationships between the frequency of defecations and HRQoL, clinical data, or laboratory tests results.

Authors, reference	HRQoL	Laboratory data	Clinical data
Ruszkowski [18,27]	Defecation less frequently than mean once a day was significantly associated with worse assessment of physical functioning, role limitations due to physical health problems, and mental health. Additionally, having less than 7 BM/week was associated with the increased prevalence ratio of impaired sleep quality (PR 7.23, 95% CI 1.74-30.12, *P* = 0.007) in comparison to having 7 BM/week. After adjustment for key clinical data, the association remained significant (PR 4.64, 95% CI 1.13-18.97, *P* = 0.03).	NR	NR
Ohkuma [26]	NR	In patients with diabetes type 2, the likelihood of both decreased eGFR (< 60 ml/min/1.73 m^2) and albuminuria (> 30 mg/g) was significantly higher in participants with less than 3 defecations per week compared with those without, with multivariable-adjusted ORs of 1.58 (1.19–2.09) and 1.49 (1.17-1.90), respectively.	NR
Ohkuma [26]	NR	In patients with diabetes type 2, the likelihood of decreased eGFR (< 60 ml/min/1.73 m^2) was significantly higher in participants with less than 7 but at least 3 defecations per week compared with those without, with multivariable-adjusted OR of 1.37 (1.16–1.62). The likelihood of albuminuria did not significantly differed between groups.	NR
Meade [29]	NR	NR	In the combined group of non-dialysis and dialysis CKD patients, "there was no significant association of fruit, vegetables, wholegrains or legumes intake with (...) stool frequency" (*P* not reported).

Table S23. Sensitivity analysis: differences from the reference model exceeding one percent.

Outcome	Subgroup	Model	Overall proportion (prevalence)			Difference in proportion
			Point estimate	95% CI: LL	95% CI: UL	
Self-reported diarrhea	G4-5	cauchit	0.1533	0.1173	0.2167	-0.0244
Self-reported abdominal pain	G4-5	cauchit	0.1724	0.0898	0.5401	-0.0232
Functional constipation	G3	FTT (ML, harmonic)	0.1543	0.0714	0.2557	-0.0191
Functional constipation	G3	FTT (REML, harmonic)	0.1543	0.0714	0.2557	-0.0191
Self-reported abdominal bloating	G4-5	cauchit	0.3467	0.2475	0.4906	-0.0147
Self-reported diarrhea	G3	cauchit	0.1240	0.0857	0.2153	-0.0134
Self-reported diarrhea	G1-2	FTT (ML, harmonic)	0.1258	0.0283	0.2607	-0.0127
Self-reported constipation	G4-5	cauchit	0.3747	0.3033	0.4620	-0.0130
Self-reported abdominal pain	G4-5	FTT (ML, harmonic)	0.2075	0.0619	0.4023	0.0120
Self-reported abdominal bloating	G1-2	FTT (REML, harmonic)	0.4971	0.4010	0.5933	0.0127
Self-reported abdominal bloating	G1-2	FTT (REML, inverse var)	0.4972	0.4032	0.5913	0.0127
Self-reported diarrhea	G4-5	FTT (ML, inverse var)	0.1907	0.1437	0.2425	0.0130
Self-reported abdominal pain	G4-5	FTT (REML, harmonic)	0.2085	0.0386	0.4525	0.0130
Self-reported diarrhea	G4-5	FTT (REML, inverse var)	0.1909	0.1427	0.2441	0.0131
Self-reported diarrhea	G1-2	FTT (ML, inverse var)	0.1572	0.0623	0.2816	0.0186
Self-reported diarrhea	G1-2	FTT (REML, inverse var)	0.1658	0.0403	0.3429	0.0273

Supplementary Figures

Figure S1. Funnel and Doi plot for self-reported constipation in chronic kidney disease (CKD) G4–5

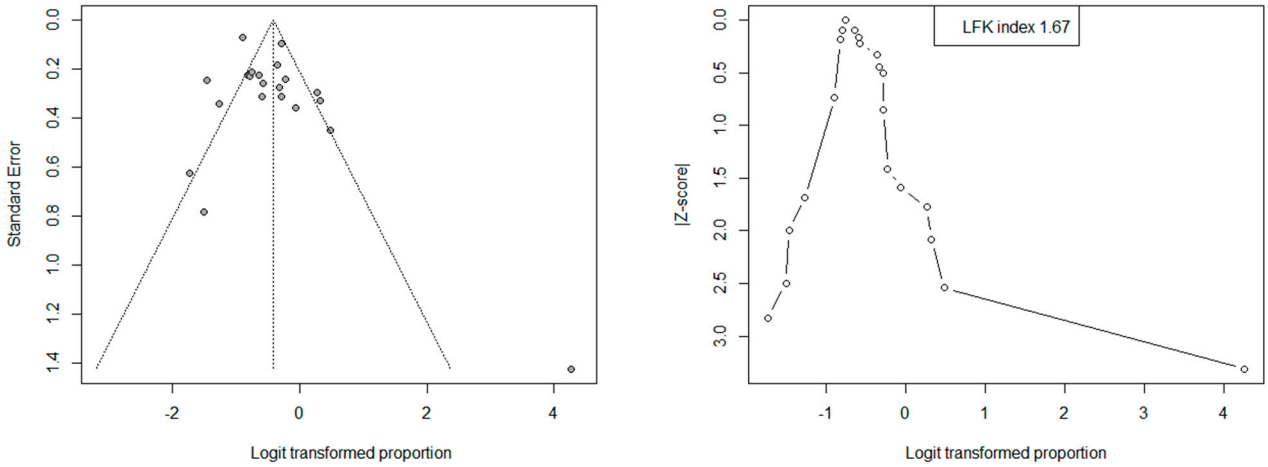
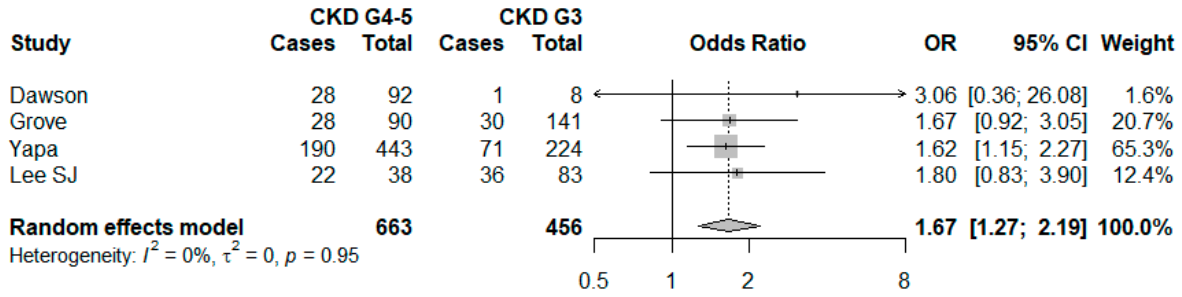
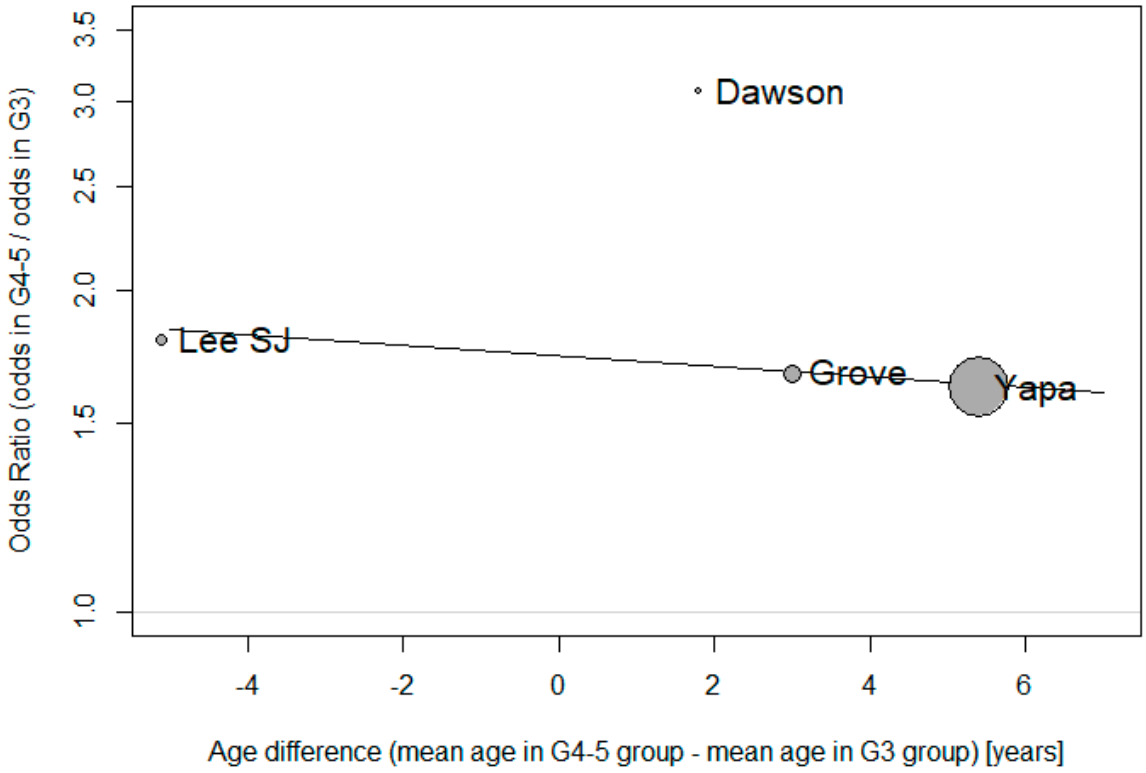


Figure S2. Forest plot with pooled odds ratio for self-reported constipation in CKD (G4–5 vs G3)



Random effects model with restricted maximum-likelihood (REML) estimator for τ^2. The weighted pooled OR significantly differs from 1 ($P < 0.001$).

Figure S3. Bubble plot based on meta-regression model: odds ratio for self-reported constipation in CKD (G4–5 vs G3)



Meta-regression conducted using mixed-effects model (k = 4; τ^2 estimator: REML, R^2 = 0%). Estimated effect of the age difference: -0.0114 [95% CI: -0.0916 to 0.0688], *P* = 0.78.

Figure S4. Funnel and Doi plot for self-reported diarrhea in CKD G4–5

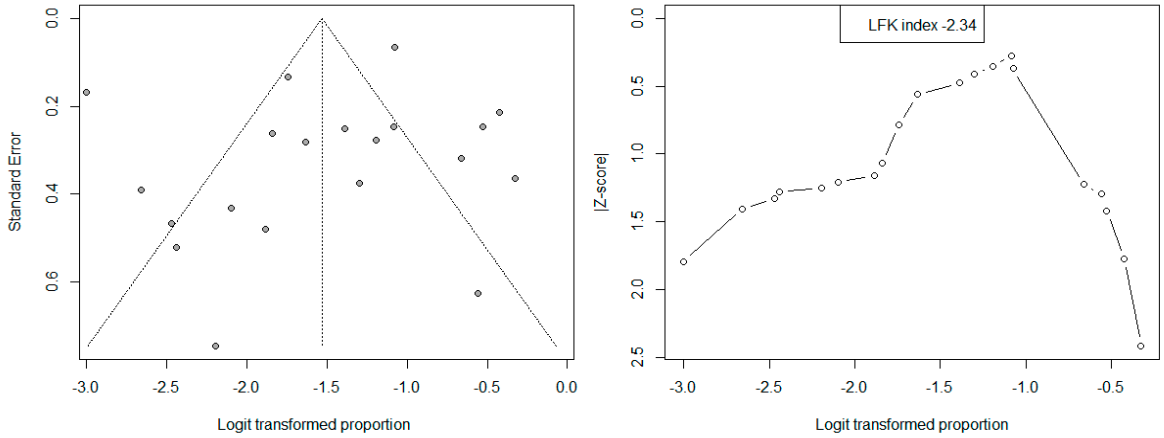
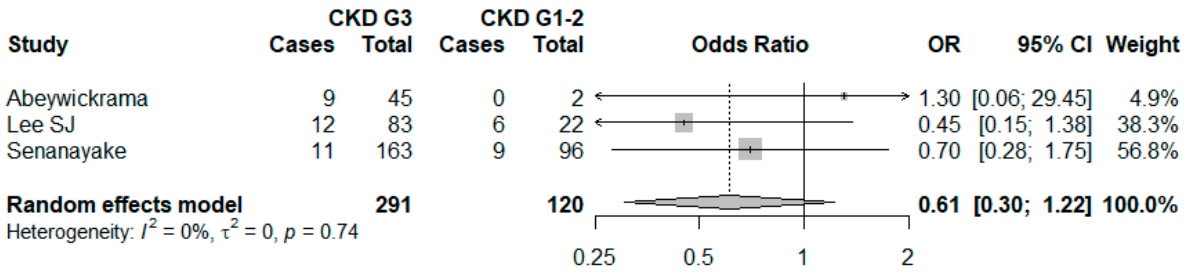
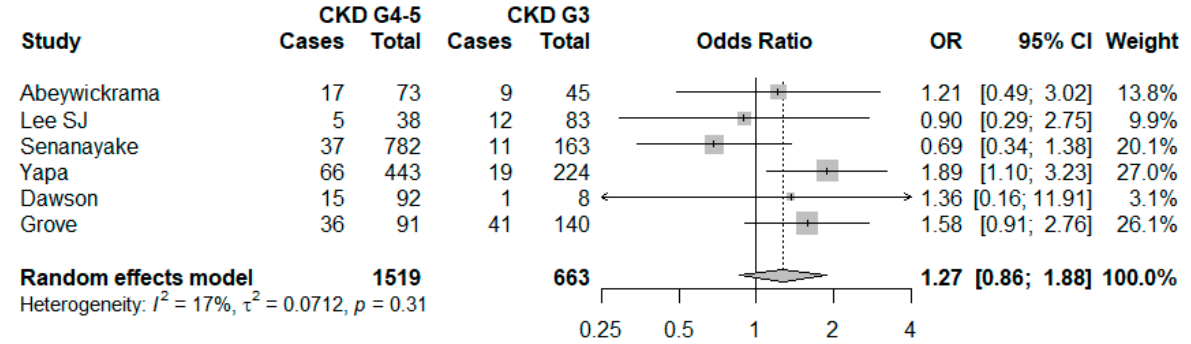


Figure S5. Forest plot with pooled odds ratio for self-reported diarrhea in CKD (G3 vs G1-2)



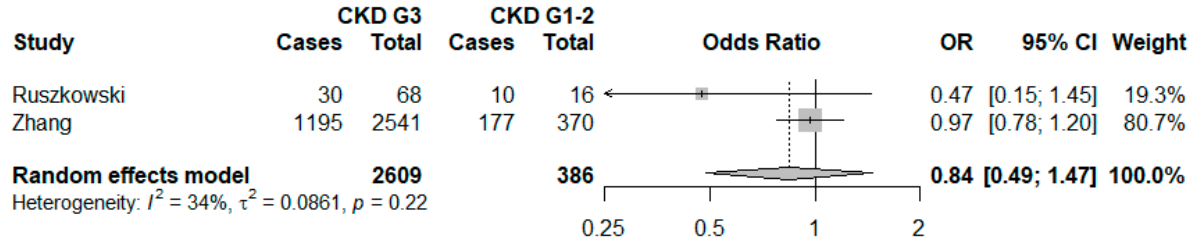
Random effects model with restricted maximum-likelihood (REML) estimator for τ^2. The weighted pooled OR does not significantly differ from 1 (P = 0.16).

Figure S6. Forest plot with pooled odds ratio for self-reported diarrhea in CKD (G4-5 vs G3)



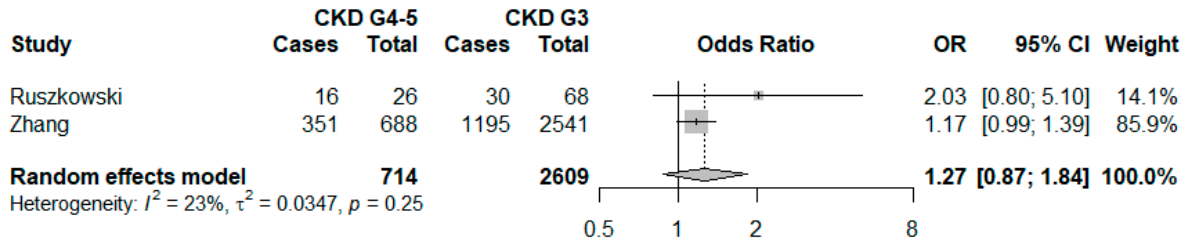
Random effects model with restricted maximum-likelihood (REML) estimator for τ^2. The weighted pooled OR does not significantly differ from 1 (P = 0.23).

Figure S7. Forest plot with pooled odds ratio for self-reported abdominal bloating in CKD (G3 vs G1–2)



Random effects model with restricted maximum-likelihood (REML) estimator for τ^2. The weighted pooled OR does not significantly differ from 1 (P = 0.55).

Figure S8. Forest plot with pooled odds ratio for self-reported abdominal bloating in CKD (G4–5 vs G3)



Random effects model with restricted maximum-likelihood (REML) estimator for τ^2. The weighted pooled OR does not significantly differ from 1 (P = 0.21).

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