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Efficacy of erythropoietin as a neuroprotective agent in CKD-associated cognitive dysfunction: A literature systematic review

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ABSTRACT

Patients with chronic kidney disease (CKD) often experience mild cognitive impairment and other neurocognitive disorders. Studies have shown that erythropoietin (EPO) and its receptor have neuroprotective effects in cell and animal models of nervous system disorders. Recombinant human EPO (rHuEPO), commonly used to treat anemia in CKD patients, could be a neuroprotective agent. In this systematic review, we aimed to assess the published studies investigating the cognitive benefits of rHuEPO treatment in individuals with reduced kidney function. We comprehensively searched Pubmed, Cochrane Library, Scopus, and Web of Science databases from 1990 to 2023. After selection, 24 studies were analyzed, considering study design, sample size, participant characteristics, intervention, and main findings. The collective results of these studies in CKD patients indicated that rHuEPO enhances brain function, improves performance on neuropsychological tests, and positively affects

Abbreviations: ADL, activities of daily living; CAPD, continuous ambulatory peritoneal dialysis; CKD, Chronic Kidney Disease; COWAT, Controlled Oral Word Association Test; CRF, chronic renal failure; EPO, erythropoietin; ESRD, end-stage renal disease; Hb, Hemoglobin; Hct, hematocrit; HRQOL, Health-Related Quality of Life; IADL, instrumental activities of daily living; KDQ, Kidney Disease Questionnaire; KF, kidney failure; LASA scale, Linear analog self-assessment scale; MCS, mental component score; MMSE, Mini-Mental State Examination; PCS, physical component score; QoL, quality of life; RAVLT, Rey Auditory Verbal Learning Test; RCMRO2, metabolic rate for Oxygen; RDT, regular hemodialysis treatment; SDMT, Symbol Digit Modalities Test; SF-36, Short Form Health Survey 36; TMTA, Trail Making Test A; TMTB, Trail Making Test B; TOL, Tower of London; WMS, Wechsler Memory Scale.

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electroencephalography measurements. These findings suggest that rHuEPO could be a promising neuroprotective agent for managing CKD-related cognitive impairment.

1. Introduction

Chronic kidney disease is an important and common public health problem that affects 10–15 % of the world's population [1] and it is associated with an impaired quality of life and substantially reduced life expectancy at all ages [2]. Previous studies have shown that the prevalence of cognitive decline in people with kidney failure (KF) is more than twice that in the age-paired general population [3] and that the probability of developing cognitive decline increases as CKD progresses in severity [3] Distinct cognitive domains, such as memory disorders, coordination, executive functioning, reasoning, focusing, and language are defective in patients with CKD [4]. The exact mechanism for neurocognitive dysfunction in CKD is not known. Among several specific CKD-related factors, anemia is held as an important risk factor for cerebral dysfunction in CKD patients [5,6].

Erythropoietin (EPO) is a glycoprotein hormone and hematopoietic cytokine mainly induced by hypoxia conditions. It is produced in the kidney and primarily activates erythroid cell production by enhancing erythroid progenitor cell proliferation, survival, and differentiation [7]. Reduced EPO synthesis in the diseased kidneys underlies low hemoglobin (Hb) levels in CKD patients [8].

Several studies have revealed that recombinant human EPO (rHuEPO), commonly clinically used to treat secondary anemia in both CKD and cancer patients, has additional therapeutic benefits for a wide variety of neurological diseases from Alzheimer's disease, dementia, and Parkinson's disease to schizophrenia and cerebrovascular disease [9–12]. In this regard, EPO has been shown to have both neurotrophic and neuroprotective effects. In order to characterize the processes through which EPO affects the central nervous system, *in vitro* and *in vivo* studies have been performed [13–16]. rHuEPO interacts with four different isoforms of its receptor (erythropoietin receptor [EPOR]), triggering distinct signaling pathways with several roles in neuroprotection and the development of nervous tissues [15]. The neuroprotective action of EPOs includes decreased neuronal death, reduced inflammation[17], oligodendrocyte differentiation and maturation, and enhanced white matter integrity [18].

The first evidence suggesting that rHuEPO might improve brain functions in individuals with reduced kidney function came to light from studies in patients on hemodialysis and peritoneal dialysis on treatment with rHuEPO that documented improved cognitive functions in these populations [13,14]. In particular, two randomized, double-blind studies evaluated the effects of rHuEPO treatment on brain function and demonstrated that administration of rHuEPO led to higher performance in an intelligence quotient (IQ) test and improved brain function measured by electrophysiological parameters [13,14]. These observations stimulated studies aiming to analyze the effect of this medication on the brain.

To assess the strength of the present evidence, we performed a systematic review of studies focusing on the potential benefits of rHuEPO treatment on cognitive function in patients with CKD. The primary cognitive outcomes assessed were: a) the scores of the main neuropsychological tests, b) electrophysiological markers, c) Health-Related Quality of Life (HRQoL) mental health score, d) risk for dementia, e) levels of dementia molecular markers (GSK3β, Aβ, total Tau, p-Tau 181) and brain metabolism.

2. Materials and methods

2.1. Search strategy

Following PRISMA guidelines, systematic search from 1990 to May 2023 has been conducted in Pubmed, Cochrane Library, Scopus, and Web of Science with the research expression (Erythropoietin OR "Erythropoietin" [Mesh]) AND (kidney diseases OR "Kidney Diseases" [Mesh] OR "Kidney "[Mesh]) AND ("Cognition" [Mesh] OR "Dementia" [Mesh] OR Cognitive OR dementia OR brain). In addition, conference records and unpublished literature were retrieved using Google Scholar, EThOS, the British Library Catalogue, OpenGrey, and Copac theses. We utilized backward and forward citation tracking to collect relevant studies and review records.

2.2. Eligibility

Inclusion criteria were built using PICOS, as presented in Table 1. Two authors (P.D.G., G.T.) screened the titles and abstracts to identify articles reporting on the effects of rHuEPO on cognitive function in patients with CKD. The review included only original articles in the English language, encompassing observational studies and randomized trials.

Epoetin alfa, Epoetin beta, Epoetin zeta, Darbepoetin alfa, and Methoxy polyethylene glycol-epoetin beta are all recombinant erythropoiesis-stimulating agents with different glucosylation patterns but with similar mechanism of action. Studies were not included if they met one of the following conditions: (1) non-research-based articles, such as conference abstracts, review articles commentaries, opinion pieces, book chapters, and editorials; (2) case series with fewer than three cases; (3) abstract was not available; (4) or full text was not available, 5) studies with only *in vitro* procedures, in animals studies or 6) studies including neurological diseases different from dementia.

2.3. Data extraction, analysis, and quality assessment

Data from each study, including study specifics, participant demographics, and fundamental results, were extracted into a spreadsheet. The primary outcome measures were initially intended to be the change in neuropsychological scores. Nevertheless, given the relatively small number of eligible studies and their heterogeneity, a descriptive-analytical method was utilized for the current review.

3. Results

3.1. Study selection

Among the 560 articles, the Web of Science® Core Collection database investigation retrieved 214 results, PubMed 198 results, Scopus retrieved 102 results, and Cochrane Library retrieved 46 results. After duplicate removal (n = 110), 452 articles were screened by title, and if the title was inconclusive, the abstracts were read. After careful selection, 67 articles were chosen for full-text reading. Finally, based on our inclusion and exclusion criteria, 42 articles were eliminated for not meeting eligibility criteria, and 24 articles met the criteria for qualitative analysis (Fig. 1). Twelve studies were conducted on patients on hemodialysis. The primary cognitive outcomes included: scores of Mini-

Table 1
Inclusion criteria for the systematic review.

P	Patients with at least one diagnosis of CKD or KF
I	Studies that include a potential role of rHuEPO treatment on different cognitive function parameters in patients affected by CKD or KF
C	Compared to a placebo or other treatments
O	Change in neuropsychological scores
S	Published original articles, observational studies, randomized clinical trials

Mental State Examination (MMSE), Wechsler Memory Scale – I (WMS-I), Tower of London (TOL) test, Wechsler Adult Intelligence Scale-Revised (WAIS-R), Controlled Oral Word Association Test (COWAT), Symbol Digit Modality Test (SDMT), Rey auditory verbal learning test (RAVLT), Trail Making Test - part A (TMTA) and TMTB (Trail Making Test - part B), variation in electrophysiological markers of cognitive function, HRQoL (Health-Related Quality of Life) mental health score, risk of dementia, and levels molecular markers of dementia (GSK3β, amyloid β (Aβ), total Tau, p-Tau 181).

3.2. Overview of included studies

The studies included for this systematic review were published from 1989 to 2019. Fifteen studies were observational studies, and nine were RCTs (Table 2). In the following sections, we describe the results of these studies grouped according to the outcomes and measures adopted in the same studies.

3.3. Neuropsychological assessment

Table 3 summarizes the main neuropsychological tests measured in the 24 studies analyzed.

In a non-randomized study [14], nine patients on chronic peritoneal dialysis received rHuEpo treatment and underwent psychometric tests before and after partial correction of anemia. Eight patients, matched for age, duration of dialysis, and social class, did not receive rHuEpo and also underwent the same tests. The rHuEpo-treated group showed significant improvement in the Intelligence Quotient (IQ) and concentration/speed of information processing. Memory also tended to improve in this group. No significant changes were observed in the control group. Information processing speed, assessed by the Paced Auditory Serial Addition Task, improved in the treatment group, and this improvement was accompanied by higher memory scores, which were evaluated by the RAVLT. No overall difference was noted in both groups in the time necessary to complete the TMTA [19], a test assessing concentration, psychomotor speed, visual scanning, and the ability to sequence.

In an uncontrolled study of twenty-four hemodialysis patients treated with rHuEPO to correct anemia [20], hematocrit levels reached normal values after three months. Neurological assessments at six months showed significant improvements in brain event-related potentials and neuropsychological test scores, indicating enhanced cognitive function. In another study [21] that adopted the TMTB [19], a more complex form of trail-making test, no differences in time to completion

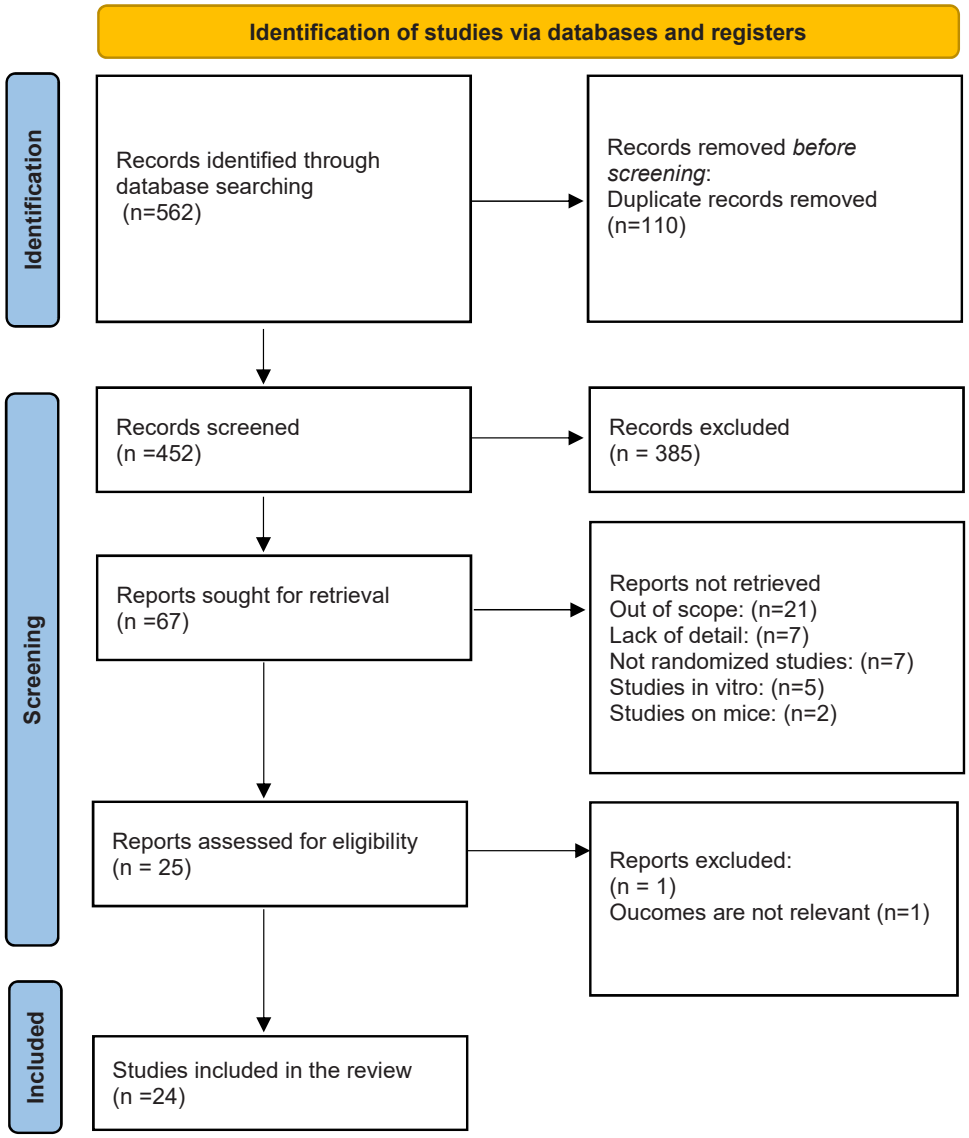

Fig. 1. Prisma Diagram.

Table 2
Overview of included studies (n = 24).

Authors and year of publication	Objective	Type of study	Participants	Intervention	Control	Outcome	Results	Risk of Bias
Wolcott et. al. (1989)	Evaluate the effect of rHuEPO treatment on psychological, longitudinal medical and social adaptation (quality of life) as well as cognitive function.	Observational Cohort Study	RDT (n = 15)	rHuEPO treatment		COWAT, WAIS at BL, 1 month after Hct normalization and 10–15 months after.	↓ fatigue = cognitive functions.	Moderate
Grimm et. al. (1990)	Evaluate the effects of anemia and its partial correction on brain dy sfunction by rHuEPO treatment	Observational Case-Control Study	Chronic hemodialysis patients with transfusion-dependent anemia (n = 21)	rHuEPO treatment (n = 15)	Subjects not treated with rHuEPO (n = 6)	TMTA and event-related P300 evoked potentials before and after rHuEPO treatment.	↑ P300 peak latency and amplitude ↓ time in completing TMTA	Low
Marsh et. al. (1991)	Assess the effects of rHuEPO treatment on the efficiency of cognitive functioning using both electrophysiological and neuropsychological measures.	Observational Cohort Study	Patients with KF (n = 24)	rHuEpo treatment		Electrophysiological methods: P300 amplitude and latency. Neuropsychological measures: COWAT, SDMT, RAVLT, TMTB	↑ P3 amplitude increased in 17 of 22 patients (77 %) TMTB and SDMT improved. RAVLT and COWAT failed to reach a statistical significance.	Low
Brown et. al. (1991)	Investigate the relationship between P3 latency and amplitude, neurocognitive performance and mood in a group of dialysis patients after rHuEPO treatment.	Observational Cohort Study	Patients in ESRD on hemodialysis (n = 14)	rHuEpo		Neuropsychological measures: COWAT, TMTA, TMTB, SMDT, RAVLT, WAIS before treatment and after 12 months of treatment Electrophysiological methods: P300 amplitude and latency before treatment and after 12 months of therapy with rHuEPO	↑ Neurocognitive tests ↑ P3 amplitude in frontal areas, = P3 latency.	Low
Di Paolo et. al. (1992)	Evaluate the electrophysiologic responses of the central nervous system in patients on RDT.	Observational Case-Control Study	Patients on chronic RTD with transfusion-dependent anemia	Patients on r-HuEPO treatment (n = 18)	Healthy subjects (n = 10)	P100 latency at BL, 12 weeks and 24 weeks	↓ P100 latency from BL to 24 weeks.	Low
Temple et. al. (1992)	Investigate cognitive function in a group of haemodialysis patients treated with rHuEpo and an equal number of matched control patients.	Observational Case-Control Study	Haemodialyspatients (n = 18)	Anaemic patients treated with rHuEpo (n = 9)	Anaemic patients not treated with rHuEpo (n = 9)	WAIS-R at BL and when a Hb more then 9.0 g dl was achieved after a minimum of 12 weeks treatment	↑ WAIS-R score in the treated group	Low
Hirakata et al. (1992)	Investigate the hypothesis that correction af anemia with rHuEPO can improve the Cerebral oxygen metabolism	No-RCT Interventional Case-Control	Hemodialysis patients	rhEPO treatment (n = 5)	Non demented and non-anemic patients (n = 8)	$rCMRO_2$,rCBF, rOEF,	↓ rCBF and rOEF after rHuEPO treatment No differences with $rCMRO_2$ after treatment	Low
Sagalés et. al. (1993)	Evaluate the effects of treatment with rHuEPO on brain function in patients with CKD.	Observational Case-Control Study	Patients in hemodialysis treatment for six month prior to initiation of the study	Patients on r-HuEPO treatment (n = 43)	Healthy volunteers (n = 8)	P300 latency and amplitude	↓ P300 latency.	Low
Di Paolo et. al. (1993)	Evaluate the role of rHuEPO treatment in improving the electrophysiological brain function in uremic and anemic patients.	Interventional Cohort study	CAPD patients with Severe anemia (n = 9)	4000 U rHuEPO once weekly (n = 7)	4000 U every 5 and 8 days, 1 patient received 4000 U every 10 days. (n = 2)	Evoked potentials: visual (VEP), brainstem auditory (BAER), and somatosensory (SEP)	Improved electrophysiological potentials.	Moderate
Temple et al. (1995)	Investigate cognitive function in patients on CAPD treated with rHuEpo compared to control patients	Interventional Case-Control	CAPD Patient (n = 17)	rHuEpo treatment (n = 9)	Patients not on rHuEpo treatment (n = 8)	WAIS-R Score; Paced Auditory Serial Addition Task; Rey Auditory Verbal Learning Test	↑ IQ by a mean of 7.2 points. In the control group no significant improvement was demonstrated. ↑ Memory and concentration	Low

(*continued on next page*)

Table 2 (*continued*)

Authors and year of publication	Objective	Type of study	Participants	Intervention	Control	Outcome	Results	Risk of Bias
Revicki et. al. (1995)	Compare changes in HRQL in r-HuEPO-treated and untreated predialysis chronic renal disease patients with anemia.	RCT Interventional Case-Control	Predialysis renal disease patients. (n = 83)	rHuEpo (n = 43)	Supportive treatment (n = 40)	HRQL assessment at BL, 16 weeks and 48 weeks	↑ Energy, physical function, home management, social activity and cognitive function in the r-HuEPO-treated group.	Low
Beusterien et. al. (1996)	The study explores the relationship between hematocrit levels and HQoL.	Observational Case-Control Study	Dialysis patients (n = 1004)	New to Epo patients (n = 484)	Old to Epo patients (n = 520)	SF-36 scales on Physical functioning, social functioning, mental health. BL and 99 days (mean) after.	↑ in the new to Epo patients from baseline to follow up. No great changes in the old to Epo group.	Moderate
Pickett et. al (1999)	Assess effects of anemia on brain function in dialysis patients after correction of anemia to near-normal Hct values with rHuEPO	Observational Cohort Study	Patients with ESRD currently treated with rHuEPO and receiving regular dialysis treatments. Hct was less than 35 % in all patients	rHuEPO (n = 20)		P300 latency and P300 amplitude. T1: Baseline T2: 2–3 weeks after 40–45 % Hct achieved	↓ EEG slowing at greater Hct values, the auditory oddball and Continuous Performance Task tasks showed significant electrode and time-by-electrode effects for P300 amplitude. ↓ P300 latency with increased Hct.	Moderate
Lee SY et al. (2004)	To examine the association between levels of hematocrit and improvement of cognitive function as well as quality of life in patients with end-stage renal disease	Observational Case-Control Study	Patients with ESRD (n = 56)	rHuEpo for hematocrit levels < 27.2 g % (n = 28)	rHuEpo for hematocrit> 27.2. g % (n = 28)	Quality of life: Karnofsky Scale, Index of Well-Being, and SF-36 Neurocognitive tests: Forward digit–span and digit–symbol	↑ scores in neurocognitive tests; their = QoL compared to the lower hematocrit group.	Moderate
Singh et. al. (2006)	Study the effect of improvement in anemia on event-related potentials (ERPs; P300) as markers of cognitive dysfunction in predialysis and dialysis patients of CKD.	Observational Case-Control Study	Anemic patients with CKD. Group A: predialysis group. Group B: dialysis group. Group C: healthy controls	Groups A and B treated with rHuEpo (n = 15+15)	Group C: healthy volunteers (n = 30)	P300 latency and P300 amplitude	↓ P300 latency after intervention. Similarly, the amplitude of P300 also increased in both study groups, but attained statistical significance for the dialysis group only.	Low
Sing et al. (2006)	Evaluate whether the use of epoietin alfa can decrease cardiovascular risk and improve QoL.	RCT Interventional Case-Control	1432 CKD patients	Patients receiving epoietin alfa to achieve a Hb of 13.5gr/dL (n = 715)	Patients receiving a epoietin alfa to achieve a Hb of 11.3gr/dL (n = 717)	LASA, KDQ, SF-36 scores	No differences in the QoL was noted in thestudy groups.	Low
Drüeke et al. (2006)	Evaluate whether complete correction of anemia in CDK patients improves cardiovascular risk and QoL	RCT Interventional Case-Control	605 CKD patients	Patients receiving immediate treatment with epoietin beta (n = 301)	Patients receiving epoietin beta only if Hb level was 10.5gr/dL (n = 302)	SF-36 scores	↑ SF-36 scales at year 1: Global health, mental health, physical role, social functioning, vitality	Low
Alexander et. al. (2007)	Assess the association of changes in Hb with changes in health- related quality of life (HRQOL).	RCT Interventional Case-Control	CKD patients not on dialysis nor expecting to initiate dialysis (n = 81)	Patients receiving darbepoetin alfa plus conservative management of CKD (n = 62)	Dialysis patients (n = 19)	SF-36, FACT-anemia, FACT-fatigue, ADL and IADL) at BL, 8 weeks, 16 weeks	↑ HRQOL subscales concerning activity, vitality and fatigue in the treatment group.	Low
Ali K. Abu-Alfa et al. (2008)	Evaluate the effect of darbepoetin alfa on Hb levels and HRQoL measures in subjects with CKD who are naïve to erythropoiesis-stimulating agents	Observational Cohort study	Patients with CKD not receiving dialysis treatment	Patients with darbepoietin treatment (n = 277)		MCS, PCS, Kidney Disease Burden, Kidney Disease Effect, and Kidney Disease Symptom scores at BL, week 12 and 52	↑ scores between baseline and week 12 and these improvements were maintained through week 52.	Low
Lewis et. al. (2011)	Evaluate the effect of darbepoetin alfa on HRQOL, with a focus on three prespecified domains: fatigue, energy, and physical function.	Observational Cohort study	Patients with type 2 diabetes mellitus, CKD not on dialysis, and anemia.	Darbepoetin alfa (n = 2295)		Change in SF-36 Mental Health after 25, 49 and 97 weeks	↓ Fatigue ↑ QoL	Low

(*continued on next page*)

Table 2 (*continued*)

Authors and year of publication	Objective	Type of study	Participants	Intervention	Control	Outcome	Results	Risk of Bias
Plantinga et.al. (2017)	Examine whether Hb concentration after 6 months of hemodialysis was associated with QOL at 1 year.	Observational Cohort Study	Patients in hemodialysis (n = 465)	Patients with Hb > 11 g/dL at 6 months (n = 169)	Patients with Hb < 11 g/dL at 6 months (n = 296)	QoL scores	↑ QOL at 1 year, with regard to physical, mental, social, and cognitive domains in patients with higher Hb concentration at 6 months	Low
Vinothkumar et.al (2018)	Impact of rHuEPO therapy on platelet APP, BACE 1, ADAM10, presenilin 1, Aβ and platelet rich plasma LPO level.	Interventional Case-Control Pilot Study	CKD Patients (n = 60)	Patients with cognitive Dysfunction treated with rHuEpo (n = 30)	Patients without cognitive dysfunction (n = 30)	APP, BACE1, Presenilin 1, ADAM 10 and Aβ expressions in platelets were determined by western blotting	↓ APP, ADAM 10 ↑ BACE1, Presenilin 1, Aβ in CKD with cognitive dysfunction subjects compared to control	Low
Vinothkumar et.al (2019)	Study the correlation between rHuEPO therapy on platelet GSK3b expression, total Tau, p-Tau 181 levels and neuropsychological assessments total scores in CKD patients with Cognitive dysfunction.	Interventional Case-Control Pilot Study	CKD Patients (n = 60)	Patients with cognitive Dysfunction treated with rHuEpo (n = 30)	Patients without cognitive dysfunction (n = 30)	MMSE, WMS, TOL scores. Baseline and six months after treatment	↑ neuropsychological assessment scores compared to pre-treatment.	Low
Hung et. al. (2019)	Evaluation of EPO and/or Iron intake on general risk of dementia and subtypes	Observational Case-Control Study	Patients in hemodialysis	Patients with rHuEpo and without Iron (n = 26441)	Patients without rHuEpo and Iron (n = 5789)	Adjusted HR (95 % IC) for dementia	↓ likelihood of developing dementia in patients treated with rHuEPO and iron.	Low

EPO: erythropoietin, SF-36: Short Form Health Survey 36, CKD: Chronic Kidney Disease, MMSE: Mini-Mental State Examination, WMS: Wechsler Memory Scale, TOL: Tower of London, QoL: quality of life, HRQOL: Health-Related Quality of Life, ADL: activities of daily living, IADL: instrumental activities of daily living, ESRD: end-stage renal disease, Hb: Hemoglobin, Hct: hematocrit, CAPD: continuous ambulatory peritoneal dialysis, CRF: chronic renal failure, RDT: regular hemodialysis treatment, COWAT: Controlled Oral Word Association Test, SDMT: Symbol Digit Modalities Test, RAVLT: Rey Auditory Verbal Learning Test, rCMRO2: metabolic rate for Oxygen, LASA scale: Linear analogue self-assessment scale, KDQ: Kidney disease Questionnaire, TMTA: Trail Making Test A, TMTB: Trail Making Test B, MCS: mental component score, PCS: physical component score

Table 3
Neuropsychological tests measured in the 24 studies analyzed.

Neuropsychological tests	Cognitive domain
MMSE (Mini-Mental State Examination)	Attention, orientation, memory, registration, recall, calculation, language and ability to draw a complex polygon.
WMS (Wechsler Memory Scale);	Auditory memory, visual memory, visual working memory, immediate memory and delayed memory
TOL (Tower of London);	Executive functioning, including problem-solving skills, planning ability, cognitive flexibility, and working memory
COWAT (Controlled Oral Word Association Test)	Cognition lexical retrieval, semantic memory, cognitive flexibility, and executive control, language skills, verbal fluency, and cognitive efficiency.
SDMT (Symbol Digit Modalities Test)	Attention, visual scanning, processing speed, and working memory.
RAVLT (Rey auditory verbal learning test)	Verbal learning and memory, including immediate recall, learning curve, retention, and recognition memory
TMTA (Trail Making Test Part A)	Processing speed and attention
TMTB (Trail Making Test Part B)	Executive function

were registered after three months of treatment with rHuEPO. A significant improvement in this test was evident after 12 months of therapy, suggesting that the positive effects of rHuEPO on cognitive function may require long-term treatment. In the same study, the impact of rHuEPO treatment on mean scores of the SDMT [22], the RAVLT [23], and COWAT [23] were evaluated. After three months of rHuEPO administration, a significant increase was noted in the SDMT score, while the scores for RAVLT and COWAT failed to achieve significance. The SDMT score showed a further improvement at 12 months while the other tests did not show significant changes.

In another uncontrolled study [24], rHuEPO improved neuropsychological test scores in fourteen hemodialysis patients with mild cognitive deficits. In particular, neurocognitive functioning improved in complicated speeded perceptual-motor tasks that require precise scanning and mental manipulation. In contrast, measures of cognitive power (COWAT, Arithmetic), which were unaltered at baseline, remained unmodified.

Similarly, in a study that enrolled thirty CKD patients with cognitive dysfunction and an unspecified degree of kidney dysfunction [4], rHuEPO therapy for six months improved three tests of cognitive function MMSE [25], the WMS [26] and the TOL [27] test.

In a case-control study in fifty-six KF patients [28], twenty-eight patients with Hct >27 % showed better scores in the digit-symbol and forward digit-span than twenty-eight patients with Hct <27 %. However, the quality of life, as evaluated by three scales (SF-36, Karnofsky Scale, and Index of Well-Being) was similar in the two groups.

Treatment with rHuEPO to correct hematocrit to near-normal levels in twenty four KF patients [20] ameliorated levels of sustained attention, speed and efficiency of scanning and perceptual-motor functions and improved learning and memory scale scores alongside < 0.001).

3.4. Electrophysiological markers of cognitive function

Quantitative EEG and cerebral mapping are useful instruments to evaluate the central nervous system deterioration during CKD. The power spectral density measures the amplitude and frequency of electrical waves starting from brain activity. A study in forty-three CKD patients registered significantly lower power spectral density in these patients as compared to age-paired healthy individuals [29]. Moreover, when power for different frequency bands was assessed in various cerebral areas (frontal, occipital, central and temporal), patients with CKD exhibited an abnormal distribution. This was reflected by a loss of the alpha activity in the occipital areas and by an anomalous reactivity to the change in recording conditions due to eyes opening and administration of rHuEPO over twelve months coherently improved these abnormalities.

Event-related potentials (ERPs) [30] are parameters which reflect cerebral functions linked with several psychological events or brain functions, such as perception of certain stimuli, assessment and decision-making. A commonly used method for eliciting and recording ERPs is the oddball task [31], where the participant mentally counts the occurrence of random target stimuli among repeated non-targets inducing a positive wave nearly 300 ms after stimulus presentation. Among the various types of ERPs, the most recent and extensively studied one is P300, which is used to assess cognitive functions [32]. Prolonged latencies of P300 indicate that the patient needs more time for cognitive processing. Similarly, reduced amplitudes of P300 typically indicate reduced attention. Of note, protracted P300 latencies for patients with CKD [31,33] and a significant reduction in P300 latencies after the start of dialysis treatment have been observed in this population. Administration of rHuEPO in anemic patients with CKD significantly improved electrophysiological markers of brain function in the form of increased amplitudes [20,21,24] and decreased latencies [21, 29,30] of P300 in predialysis and dialysis patients. By the same token, in a study that enrolled twenty KF patients [31] rHuEPO brought the hematocrit to normal levels (43 %) and improved the EEG slowing and changes in P300 latency were significantly correlated with parallel Hct changes. These findings suggest that correcting anaemia can improve neurocognitive function, particularly focusing on more manageable tasks and discriminating and holding stimuli in memory for more complex tasks.

A 24 weeks study [33] in eighteen patients undergoing hemodialysis applied three electrophysiological tests, namely, somatosensory evoked potentials (SEP), visual evoked potentials (VEP), and brainstem auditory evoked responses (BAER) to test the effect r-HuEPO on cerebral function. After 24 weeks of r-HuEPO treatment, a decrease in the P100 VEP latency was observed and this change was accompanied by a decrease in the four main components of BAER and in the P27-N35 inter time of SEP.

3.5. HRQoL (Health-Related Quality of Life) mental health score

In a parallel-group, open-label clinical trial in KF patients maintained on conservative treatment rHuEPO three times a week improved HRQoL in the active arm of the trial ($n = 43$) compared to the control arm ($n = 40$) [34]. In an analysis based on the treatment arm of another open-label trial [35] that enrolled forty-eight CKD patients on conservative treatment, darbepoetin alfa improved the SF-36 [36] (Short Form questionnaire by the RAND corporation) physical activity, vitality, general well-being, social functioning, energy, and mental health scales in CKD patients. In the open-label, multicenter National Cooperative Recombinant Human Erythropoietin Study [37], a study involving four hundred and eighty-four dialysis patients who had not previously been treated with EPO therapy and five hundred and twenty patients who were already receiving EPO therapy at the time of study enrollment, improvements across many dimensions of functional health and well-being (vitality, physical activity, social functioning, mental stability, looking after the house, socializing, hobbies, and sexual fulfilment) from baseline to follow-up were observed in patients new to EPO treatment.

The beneficial effect of darbepoetin alfa on HRQoL mental health score was also confirmed in a large prospective study assessing HRQoL outcomes in two hundred and seventy-seven pre-dialysis CKD patients [38]. In a double-blind trial, patients affected by type 2 diabetes, non-dialysis CKD, and anemia were randomly assigned to either darbepoetin alfa or a placebo. The drug showed a consistent, though slight, improvement in global quality of life and fatigue but no progress in other domains [39]. In a prospective cohort study [40] in one hundred and sixty nine hemodialysis, those who achieved levels of hemoglobin at six months higher than 11 g/dL had better HRQoL at one year with significant improvements in mental health, physical activity, physical

discomfort, diet restriction, social functioning, cognitive functioning. In the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) trial [41] seven hundred and fifteen CKD patients on conservative treatment, a dose of epoetin alfa to achieve a high level of Hb (13.5 g/dl) and seven hundred and seventeen received a dose of the same drug to achieve a lower Hb level (11.3 g/dL). The overall QoL improved in both groups, and no significant differences between the two groups were observed, indicating targeting high levels of Hb is unwarranted in CKD patients. In another randomized clinical trial (CREATE) [42] six hundred and three CKD patients maintained on conservative treatment were assigned to two groups with different hemoglobin targets (13 g/dLg to 15 g/dl for the first group and 10.5 g/dL to 11.5 g/dL for the second group). After the first year, the QoL assessed with the use of SF-36 was significantly better in the first group in several HRQoL dimensions, including mental and general health, social and physical function, physical role and vitality, and after the second year, the between-groups difference was maintained for general health and vitality. In contrast to this large trial, no improvements in global health or the performance of daily living activities were registered in an underpowered and uncontrolled study involving only fifteen chronic hemodialysis patients on rHuEPO [43].

3.6. Risk of dementia

In a retrospective study including data from forty-three thousand nine hundred and six KF patients those on treatment with rHuEPO had a 39 % lower risk of dementia compared to those untreated with this drug and concomitant treatment of rHuEPO and iron further reduced the risk of dementia [44]. In this study the use of rHuEPO of less than 71 annual defined daily doses (DDDs), 71–200 annual DDDs, and over 201 annual DDDs, in terms of cumulative dose corresponded respectively to a 28 %, 47 %, and 38 % risk decrease in dementia, as compared with not using rHuEPO group. Moreover, the likelihood of developing dementia in patients receiving hemodialysis was decreased by 50 % when treated with rHuEPO and iron.

3.7. Molecular biomarkers and brain metabolism

Several studies endorse the potential benefits of peripheral blood markers alongside neuropsychological tests for tracking treatment effects. Cognitive decline is closely linked to cerebral senile plaques (SPs) accumulation [45], primarily composed of Aβ from amyloid precursor protein (APP) via β- (BACE1) [46] and γ- (presenilin 1) secretases. Notably, a study found lower APP and ADAM 10 levels in CKD patients with brain dysfunction compared to those without, while BACE1, Presenilin 1, Aβ, and LPO levels were higher [47]. After rHuEPO treatment, these biomarkers and neuropsychological test results improved significantly. Vinothkumar et al. [4] explored the effects of rHuEPO on CKD patients with cognitive issues, focusing on platelet GSK3β expression, plasma Aβ, total Tau, and p-Tau 181. GSK3β's role in AD is pivotal as it fosters Aβ production and Aβ-induced neuronal apoptosis by phosphorylating Tau, leading to Tau hyperphosphorylation in paired helical filaments [48]. GSK3β overactivation in AD disrupts LTP and memory, especially early in the disease. This study showed that rHuEPO significantly reversed protein abnormalities in CKD patients with brain dysfunction, enhancing neuropsychological test scores. Cognitive impairment in patients is often accompanied by dysregulated brain circulation, endothelial responses, cerebral autoregulation, and reaction to vasoconstrictors[49]. Reduced cerebral blood flow can lower brain protein synthesis and contribute to ischemic damage that, alongside Aβ, exacerbates dementia[50]. Moreover, diminished metabolic activity in the brain's inferior parietal lobe and posterior cingulate/precuneus predicts the progression from MCI to AD dementia[51]. To assess rHuEPO's impact on cerebral perfusion and oxygen metabolism in hemodialysis patients, these investigators measured CBF, OEF, and rCMR02 using PET in five patients versus eight healthy controls. Hemodialysis patients received a thrice-weekly intravenous rHuEPO dose of 1500 U to achieve a 10 % Hct increase. Despite anaemia improvement with rHuEPO [52], cerebral oxygen metabolism in these patients remained low, although frontal rCMR02 increased marginally yet significantly. This may align with Marsh et al.'s findings [20], who found that P3-wave amplitude post-rHuEPO predominantly increased in the frontal lobe, suggesting enhanced brain function through increased cerebral oxygen metabolism [53].

3.8. Risk of bias assessment

ROBINS-I assessment tool [54] and RoB 2 Assessment Form [55] were used for bias assessment in non-randomized and randomized trials, respectively (Table 4). Most studies have a low risk of bias. This is due to the type of outcomes that this review focuses on. Indeed, focusing on the pre/post-treatment variation on the same subjects allowed us to overcome most of the risk of bias. The major issues were related to the presence of comorbidities such as uncontrolled hypertension and arteriosclerosis, which could bias the effect of the treatment on cognitive function [56]. It is important to note that the heterogeneity of procedures, target outcomes, and samples in the selected studies makes it difficult their comparison.

4. Discussion

This systematic review aimed to examine the available literature on the effectiveness of rHuEPO for neuroprotection in patients affected by CKD. The results from 24 distinct studies provide findings that EPO treatment improves brain function, neuropsychological test performance, and electroencephalography measurements in patients affected by CKD via retrieving protein abnormalities and restoring brain metabolism and suggest that rHuEPO can be considered a potent neuroprotective agent in CKD-associated cognitive impairment. The findings of this review are consistent with previously described processes associated with EPO-mediated neuroprotective effects [20,21,24,29,30,57].

Cognitive decline affects up to one-third of patients with ESKD [58,59] with a prevalence of 89 % of MCI in CKD patients[60]. The risk of cognitive decline rises early in the course of CKD, and several studies suggest that kidney disease accelerates the decline of cognitive functions independently of age and comorbidities such as diabetes mellitus and hypertension [61]. A sneaky change in cognitive functioning is usually the first manifestation. Most expected cognitive dysfunction observed in CKD patients include executive dysfunction, selective modifications in verbal and non-verbal abilities, confusion, reduced attention, alertness, and vacillating memory. This cognitive decline seems to be dependent on the effect of uremic toxins on neurons [62] in addition to vascular damage [63]. Nonetheless, the persistence of neurobehavioral debilitation, regardless of clinically adequate dialysis, suggests that other factors also determine cognitive dysfunction. Indeed, anemia is common among patients with CKD and, in prospective studies, has been associated with a 41–61 % higher risk for dementia in this specific category of patient [64]. These results were consistent with other findings in hemodialysis patients, indicating that anemia makes a reversible contribution to uremic cerebral dysfunction [65].

The discovery of erythropoiesis stimulating agents has revolutionized the treatment of anemic patients with CKD and almost entirely eradicated the severe anemia correlated with this disease. Interestingly, several clinical studies have noted that along with the hemoglobin level, erythropoiesis stimulating agents [13,14] also improve cognitive function.

The present systematic review of the data from studies focusing on potential benefits on cognitive function of erythropoiesis stimulating agents in patients with CKD has been performed to assess the strength of the present evidence. The primary cognitive outcomes assessed were the scores of the main neuropsychological tests, electrophysiological markers, HRQoL mental health score, risk for dementia,levels of

Table 4
Revised Cochrane risk-of-bias tool for selected studies.

	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Bias
Wolcott et al. (1989)	+	+	+	?	+	?
Grimm et al. (1990)	+	+	+	+	+	+
Marsh et al. (1991)	+	+	+	+	+	+
Brown et al. (1991)	+	+	+	+	+	+
Di Paolo et al. (1992)	+	+	?	+	+	?
Temple et al. (1992)	+	+	+	+	+	+
Sagalés et al. (1993)	+	+	+	+	+	+
Di Paolo et al. (1993)	+	+	+	+	+	+
Temple et al. (1995)	+	+	+	+	+	+
Revicki et al. (1995)	+	+	+	+	+	+
Beusterien et al. (1996)	+	+	?	+	+	?
Pickett et al. (1999)	+	+	?	+	+	?
Lee SY et al. (2004)	+	+	?	+	+	?
Singh et al. (2006)	+	+	+	+	+	+
Alexander et al. (2007)	+	+	+	+	+	+
Ali K. Abu-Alfa et al. (2008)	+	+	+	+	+	+
Lewis et al. (2011)	+	+	+	+	+	+
Plantinga et al. (2017)	+	+	+	+	+	+
Vinothkumar et al. (2018)	+	+	+	+	+	+
Vinothkumar et al. (2019)	+	+	+	+	+	+
Hung et al. (2019)	+	+	+	+	+	+
Singh et al. (2006)	+	+	+	+	+	+
Drüeke et al. (2006)	+	+	+	+	+	+
Hirakata et al. (1992)	+	+	+	+	+	+

ROB, theoretical risk of bias (the specific risk of bias would benamed in an actual Cochrane systematic review); +, low risk of bias (represented with a green circle in a Cochrane publication);−, high risk of bias (represented with a red circle in a Cochrane publication); ?, unclear risk of bias (represented with a yellow circle in aCochrane publication). For non-RCT studies ROBINS-I tool were used but reported as ROB risk of bias structure.

dementia molecular markers (GSK3β, Aβ, total Tau, p-Tau 181), and brain metabolism.

The results from 24 distinct studies suggested that in patients affected by CKD, rHuEPO treatment: a) enhances cerebral function by raising levels of concentration, thus increasing speed and efficiency of scanning and perceptual-motor functions and improving learning and memory scale scores b) improves the electrophysiological markers of cerebral function by increasing amplitudes [20,21] and reducing latencies; c) enhances many dimensions of functional health and well-being (vitality, physical functioning, social functioning, mental health) d) reduces the risk of dementia; e) reduces brain protein abnormalities (decreased in APP, ADAM10 and increased BACE1, Presenilin 1, Aβ and lipid peroxidation (LPO) and f) restores frontal oxygen metabolism.

As far as the potential mechanism involved, previous evidence suggest that both direct and indirect effects of rHuEPO on brain function and cognitive performance are implicated.

In particular, Di Paolo et al. [33] demonstrated that correcting anemia with rHuEPO significantly improves brain function, neuropsychological test performance, and electroencephalography measurements in patients on regular hemodialysis treatment. Authors hypothesized that a higher Hct level determines enhanced brain oxygen delivery, directly improving cerebral metabolism and that when the Hct improves there is a decreased delivery of uremic "toxins" to the brain. The reduced cerebral blood flow may diminish intracranial pressure and, in this way, may determine its beneficial consequences by a rheologic pathway [33]. Interestingly, although these early studies observed that normalization of hemoglobin using EPO was connected with improvements in cerebral function [13,14], other researchers have proposed that erythropoiesis-stimulating agents may determine neuroprotective effects independently of hemoglobin increase [20,21,66] and directly acting in the nervous system. Various studies have demonstrated the expression of EPO and its receptor in the nervous system [67] and that it confers neuroprotection in cells and animal models of nervous system disorders [68]. In human studies, the potential of rHuEPO treatment ranges from acute and chronic neurodegenerative diseases (stroke, Parkinson's disease, AD, amyotrophic lateral sclerosis, multiple sclerosis, neurotrauma, and perinatal asphyxia) to psychiatric disorders like schizophrenia, where neurodegenerative processes can contribute to the pathophysiology of the disease [4,9,10,69,70].

Non-erythropoietic actions of EPO include reduced neuronal death, reduced inflammation, inducing oligodendrocyte differentiation and maturation, and increased white matter integrity [7]. Indeed, EPO treatment was able to reduce cerebral decline in rats and revive defective memory in vascular dementia (VaD) rat models [71,72]. Moreover, in earlier studies, it was observed that EPO was able to reduce hippocampal neuronal loss, neuroinflammation, and cholinergic deficit in rats [73] and can work as a protective agent for neuronal cells against Aβ toxicity [74,75]. A recently published study found that EPO inhibits hippocampal and synaptic insult and neuronal death by regulating BDNF and PSD-95 expression through NMDA receptors[76]. In a study on the effect of rHuEPO on kidney damage and anemia in rats with CKD, rHuEPO administration not only ameliorates the anemia but also significantly reduces the expression of BACE1, presenilin 1, Aβ, and LPO, along with increased neuropsychological test scoring and sensorimotor and cerebral functions[77].

Based on the findings of this systematic review, rHuEPO might be considered a promising neuroprotective factor in the context of CKD-associated cognitive dysfunction. This is particularly important for CKD patients who are at increased risk of therapy adverse events. The clinical use of neuroprotective agents has been impeded by the toxicity of some of the growth factors that have proved to be effective neuroprotective factors in animal research [78,79]. Secure and well-tolerated neuroprotective agents are still absent in the clinical neuroscience field. Indeed, rHuEPO is a highly well-tolerated compound used in millions of patients. Adverse effects of treatment with rHuEPO noted in the early clinical trials included hypertension, seizures, arteriovenous fistula or shunt thrombosis, hyperkalemia, and increased risk of stroke [41,42,80,81]. For adequate organ protection using EPO, it is necessary to have a better understanding of cellular-level processes and the ability to phenotype patients for relevant factors that may affect the outcome.

In recent years, alongside erythropoiesis-stimulating agents, new molecules known as hypoxia-induced factor prolyl-hydroxylase inhibitors (HIF-PHIs) emerged in the nephrologist practice as a valid

alternative to the treatment of anemia in CKD patients. These agents work by stabilizing the HIF complex and stimulating endogenous EPO production, even in patients with end-stage kidney disease. Interestingly, the hypoxia-inducible factor, as a transcription factor, drives several hundred target genes during brain development and maintains the normal function of the adult brain by reacting to changes in tissue oxygen tension[82]. Furthermore, preischemic treatment with HIF-PHIs has been shown to protect against cerebral ischemia in vivo and in vitro via elevation of EPO, protection of the blood brain barrier, and autophagy activation of neurons. Additionally, HIF-PHI treatment improved behavioral impairments in Parkinson's disease, upregulating mitochondrial respiration and counterbalancing oxidative stress by the upregulation of Nrf-2, HO-1, and SOD2 and the prevention of dopamine and TH protein loss[83]. Thus, the effect of HIF1alpha stabilizers on cognitive function in CKD patients would also be worthy of study.

5. Limitations

The results of the present systematic review should be interpreted considering some potential limitations: 1) the small sample size of most studies 2) many of the studies presented (among those eligible from the literature based on well-defined criteria) are observational with a weak pre-post design and short duration of treatment; 3) the heterogeneity of procedures, inclusion criteria, target outcomes and the inclusion of different ethnic groups makes difficult their comparison 4) the lack of data on age and sex-related differences and the presence of comorbidities such as uncontrolled hypertension and arteriosclerosis or diabetes, could bias the effect of the treatment on cognitive function.

6. Conclusions

This systematic review suggests a neuroprotective activity of rHuEPO in the context of CKD-associated cognitive decline. rHuEPO favorably impacted several neurocognitive tests including MMSE, Karnofsky scale, Wechsler Memory Scale. Several studies using quantitative EEG and brain mapping demonstrated improved brain functions in patients treated with rHuEPO compared to controls. Considering the high heterogeneity and different methodologies of studies included in this systematic review, randomized-controlled trials adopting validated and consistent outcome measures to determine the efficacy and safety of EPO are a public health priority.

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Declaration of Competing Interest

All authors have no potential conflicts of interest to be disclosed or relevant financial interest in this manuscript.

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Appendix

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