NEFROLOGÍA. Volumen 26. Número 1. 2006

Development and use of a quality assessment scale specifically constructed for the assessment of studies that compare hemodialysis modalities

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SUMMARY

There are currently many hemodialysis modalities that are believed to be superior to conventional hemodialysis. In order to compare the effectiveness and security of the different hemodialysis techniques a systematic review was carried out. Faced with the fact that the scales available mainly focus on study design and tend to ignore external validity, a quality scale was specifically developed to assess the quality of the studies included in the review. The objective of this article is to introduce the quality assessment scale developed and present the results of its usability and applicability. The following databases were searched in order to identify the studies: MEDLINE, EMBASE, Cochrane, HTA, CRD and others. The articles obtained were selected based on previously established inclusion/exclusion criteria. The scale covers three issues: general aspects of the studies, specific aspects of the studies and patient characteristics. This scale allowed for a more accurate classification of the global quality of the studies and was reproducible. In general, those studies classified as high quality studies received the highest score and those studies classified as low quality studies received the lowest scores. The median value was 5,35 (53,5%). The intraclass correlation coefficient was 0,96. As a conclusion of this work it can be stated that currently available scales have serious limitations for the use in studies that compare different hemodialysis modalities and that the use of a scale specifically constructed for this purpose provides more accurate information on the quality of the evidence which is fundamental to interpret results and generate inferences.

Key words: ***(MeSH Terms): Renal Dialysis. Hemodiafiltration. Review. Outcome Assessment (Health Care).***

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This study has been supported through a public research grant (FIS 03/10038, convocatoria de Proyectos de Evaluación de Tecnologías Sanitarias).

DESARROLLO Y UTILIZACIÓN DE UNA ESCALA DE VALORACIÓN DE CALIDAD CONSTRUIDA ESPECÍFICAMENTE PARA EVALUAR ESTUDIOS QUE COMPARAN MODALIDADES DE HEMODIÁLISIS

RESUMEN

En la actualidad existen diversas modalidades de hemodiálisis (HD) que se cree que podrían ser superiores a la HD convencional. Para comparar la efectividad y seguridad de las diferentes modalidades de hemodiálisis se realizó una revisión sistemática. Ante el hecho de que las escalas disponibles de valoración de calidad consideran principalmente el diseño del estudio y tienden a ignorar la validez externa, se desarrolló una escala específica para medir la calidad de los estudios incluidos en la revisión. El objetivo de este estudio es presentar esta escala y su aplicabilidad. Las bases de datos en las que se realizó la búsqueda fueron: MEDLINE, EMBASE, Colaboración Cochrane, HTA, CRD y otras. Se fijaron una serie de criterios de inclusión y exclusión para los estudios obtenidos. La escala se dividió en tres apartados: características generales de los estudios incluidos, características específicas de los estudios y características de los pacientes. La escala permitió una clasificación más precisa en cuanto a la calidad global de los estudios analizados y fue además reproducible. Aquellos estudios de mayor calidad recibieron las mejores puntuaciones y los de menor calidad las puntuaciones más bajas. La puntuación mediana fue de 5,35 sobre una escala de 10 puntos. El coeficiente de correlación intraclase fue de 0,96. Las escalas de evidencia existentes presentan limitaciones si se quieren aplicar a estudios que comparen modalidades de hemodiálisis. La utilización de una escala de calidad específica proporciona una información más adecuada sobre la calidad de la evidencia que aporta cada uno de estos estudios.

Palabras clave: ***Diálisis renal. Hemodiafiltración. Revisión. Medición de resultados de servicios sanitarios.***

INTRODUCTION

Chronic renal failure (CRF) is multifactorial pathophysiologic condition that progresses with multiple clinical consequences depending on its primary etiology and on many other risk factors (age, gender, presence of co-morbidities), etc.). Together with Germany, Spain ranks first on the list of European countries with number of patients on renal replacement therapy.[1] According to the Spanish Society of Nephrology data, 4292 patients started on replacement therapy in the year 2001, which means an incidence rate of chronic renal failure of 128 pmp.[2] Of them, 87% started on hemodialysis, 12% on peritoneal dialysis, and 1% received an anticipated renal transplantation, observing important variations between the different autonomous communities. The crude mortality rate of hemodialysis patients was 13%, of peritoneal dialysis patients 10%, and of transplanted patients 1.7%. Although it seemed there was a slight diminishing trend in recent years, preliminary data from 2002 show a mortality increase.[3] Currently, there exist multiple dialysis modalities (see table I), with no clear-cut criteria on when is it convenient to use each one of them. Besides, published studies are very heterogeneous regarding dialysis settings (type of membrane, dialysis dose, session duration, water quality, etc.), and their quality is also variable.

Table I. Hemodialysis techniques[49]

Hemodialysis
– Conventional or low-flow
– High efficiency
– High-flow
Hemofiltration
Hemodiafiltration
– Biofiltration
– Acetate-free biofiltration
– With double filter
– With double filter with activated charcoal
– On line
– High-flow

The Galician Agency for Evaluation of Health Technologies (AVALIA-T) performed a systemic review to assess the effectiveness and safety of the different hemodialysis modalities and their variants.[4] The aim of this study is to propose a quality scale specifically built to assess items that compare different dialysis modalities.

METHOD

A search was done in MEDLINE, EMBASE, Cochrane, CRD (*Centre for Review and Dissemination*) and HTA (*Health Technology Assessment*), as well as in other databases of medical literature: IBECS, IME, LILACS e ISI WEB OF Knowledge. Specific search strategies were created for each database using the corresponding descriptors and adding free terms in order to make up for possible deficiencies in indexation of some papers. The search was limited to human studies published since 1990.

Article selection

Two independent investigators following pre-established selection criteria did article selection analyzing different hemodialysis modalities. For study design, only systematic reviews, meta-analysis, clinical trials, and cohort studies were considered. Only primary studies were included with a minimum number of 20 patients and a follow-up period of at least two months. Final article inclusion was reached on a consensus and data were put on evidence tables.

Study quality assessment

In order to assess the methodological quality, we have created a specific scale and the *U.S. Preventive Services Task Force* quality scale[5] has also been used to categorize the studies according to their level of scientific evidence. The scale was built by two investigators considering the recommendations included in the *NHS Centre for Reviews and Dissemination* and the *Cochrane Collaboration* guidelines.[6,7] Both investigators were expert on assessment on health technologies, with a number of years of practice, and one of them Professor of Epidemiology. A nephrologist reviewed all the assessment task, a part of which was the creation and application of the scale.

The quality scale comprises three sections: general study characteristics, specific study characteristics, and patients' characteristics. The first two sections especially refer to the internal validity of the study and the last one to the external validity. Each section was assigned a relative weight on a 10-point total score (100%). Thus, the study general characteristics represent 50%, specific study characteristics 30%, and subjects' characteristics 20%. Each section was divided in sub-sections that received a specific weight (table II).

Two assessors independently and blindly evaluated the articles. Assessor agreement was checked using the interclass correlation coefficient (ICC).[8] This coefficient is mathematically equivalent to the kappa index for continuous variables.

RESULTS

Literature search

Literature search on biomedical databases EMBASE, MEDLINE and COCHRANE yielded 1,591 literature references in total. After exclusion of studies not meeting the selection criteria based on abstract reading and duplicate deletions, 104 references were selected. Search in other databases and the manual review of references cited in the original articles yielded seven additional references. Complete reading and evaluation of all selected articles by both assessors concluded with the consensus inclusion of 35 studies: 18 compared conventional HD with high-flow HD, one compared high-efficiency HD with low-flow HD, 13 compared different hemodiafiltration (HDF) modalities with high- or low-flow HD, and 3 compared three HDF modalities between them. Three article of high-flow HD and low-flow-HD exposed different results of the same study. The selection procedure and obtained results from literature search are shown in Figure 1.

Sixty-seven percent (12/18) of the studies comparing high- and low-flow HD came from the USA and Canada. Eighty-seven point five percent (12/16) of the studies evaluating HDF came from Europe, 9 of them from Italy.

Characteristics of included studies

Regarding the design of studies comparing high- and low-flow HD, we found out that 9 were randomized controlled trials,[9-17] 5 cross-over studies,[18-22] 2 prospective cohort studies,[23,24] and 2 retrospective cohort studies.[25,26] Five studies reported mortality and morbidity outcomes,[9-11,25,26] one quality of life outcomes,[18] and 2 pyrogenicity outomes,[23,24] and the

Table II. Escala de calidad utilizada

		General study characteristics	Score Subtotal		Weight (%) 50
Study design		Randomized control trial Non-randomized control trial Prospective cohort study Retrospective cohort study	1.5 1 0.5 0		0-15
Sample size		20-50 51-100 >100	0 0.75 1.25		0-12.5
Study groups are balanced in size		Yes No	1 0		0-10
Follow-up time		2-6 months 6 months-1 year More than 1 year	0 0.5 1.25		0-12.5
		Specific study characteristics			**30**
Clinical trial	Assess one option or the other	If randomized clinical trial, randomized method is indicated and was appropriate If not randomized trial, the inclusion in one group or the other justified and appropriate?	Yes No Yes No	0.3 0 0.3 0	0-3
	Appropriate description of study population (age, gender, race, % co-morbidities, previous time on dialysis)		Yes No	0.3 0	0-3
	Inclusion and exclusion criteria are defined		Yes No	0.2 0	0-2
	Concurrent controls		Yes No	0.4 0	0-4
	Study groups are comparable at the beginning of the study by disease status and confounding factors		Yes No	0.3 0	0-3
	Was there blinding?		Yes No	0.2 0	0-2
	Was there an appropriate description of the intervention (type of membrane, dialysis dose, dialysis frequency, duration, buffer, re-usage)		Yes No	0.2 0	0-2
	Was the follow-up time similar between groups?		Yes No	0.3 0	0-3
	Comparison groups showed no differences in losses to follow-up and they did not exceeded 20% in any case		Yes No	0.4 0	0-4
	Assessment of results was similar in both groups		Yes No	0.2 0	0-2
	Statistical analysis was on an intention-to-breat basis		Yes No	0.2 0	0-2
Cohort studies	Appropriate description of study population (age, gender, race, % co-morbidities, previous time on dialysis)		Yes	0.4 No 0	0-4
	Inclusion and exclusion criteria are defined		Yes No	0.4 0	0-4
	Study groups are comparable by disease status and confounding factors		Yes No	0.7 0	0-7
	Was there an appropriate description of the intervention (type of membrane, dialysis dose, dialysis frequency, duration, buffer, re-usage)		Yes No	0.3 0	0-3
	Was the follow-up time similar between groups?		Yes No	0.5 0	0-5
	Comparison groups showed no differences in losses to follow-up and they did not exceeded 20% in any case		Yes No	0.4 0	0-4
	Assessment of results was appropriate and similar in both groups		Yes No	0.3 0	0-3
		Included patients' characteristics			**20**
Mean time on dialysis (years)	Incident patients on ESRD Patients up to 5 years on ESRD Patients on ESRD for 5-15 years Patients on ESRD for more than 15 years, or not indicated		1 0.5	1.5 0-15 0	
Co-morbidity	There is co-morbidity in more than 50% of included patients There is no co-morbidity in more than 50% of included patients			0 0.5	0-5

When no information is available for one section, the lowest value ought to be assigned.

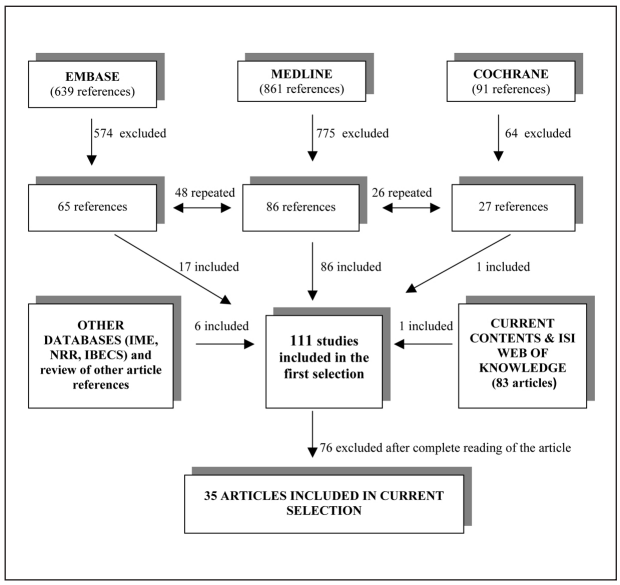

Fig. 1.—Proceso de búsqueda y selección de artículos.

remaining studies assessed several clinical consequences of CRF (anemia, nutritional status, cardiovascular risk factors, and carpal tunnel syndrome).[12-17,19-22]

Regarding the studies comparing HDF with different hemodialysis modalities or HDF studies between them, we found out that 5 were randomized trials,[27-31] 3 were pseudo-randomized or non-randomized clinical trials,[32-34] one was a prospective cohort study,[35] and 7 were cross-over clinical trials,[36-42] with no concurrent controls in three cases. The only study reporting mortality and morbidity outcomes compared conventional HDF with high- or low-flow HD.[27]

The studies were highly heterogeneous with regards to follow-up time, patients' characteristics, and dialysis technique settings. The follow-up time ranged from 2 months to 6 years, mean age of the patients ranged from 38 to 69 years, and previous time on dialysis from less than one year to more than 20. Most of the studies did not provided information enough to determine the co-morbidities ratio, although most of them excluded clinically unstable patients, and patients with serious co-morbidities. As for the dialysis technique settings, we observed that dialysis dose (Kt/V) varied from values lower than 1.2 (the minimal value recommended by the *National Kidney Foundation* clinical practice guidelines)[43] up to 1.8.

Quality assessment

According to the *U.S. Preventive Services Task Force* assessment scale, 7 out of 18 studies that compared high- and low-flow HD had a level I evidence quality, 5 a level II-1, and 4 a level II-2. According to the scale created for this review, the HEMO study reached a score of nearly 90%, and the remaining studies, excluding those by Küchle *et al.*[16] and Opatrny *et al.*,[19] did not reached a 60%-score. The only study comparing high-flow HD with conventional HD had a II-2 level but did not reached a 50%-score of our rating scale.[44]

As for the 13 studies comparing different HDF modalities with HD, 4 had level I quality, and 9 level II-1 quality. According to scores given by the two investigators, only 2 studies exceeded 60%. The studies remaining were given scores between 45% and 60%, except for one study that was given a score of around 30%. The quality of all included studies is graphically shown in Figure 2, ranked from higher to lower quality. The median score was virtually similar to the mean score (which indicates the absence of trends in assessors scoring), which was 5.35 points.

The difference between both assessors scorings was virtually naught (0.05), and was fitted a normal distribution (data checked by the Shapiro-Wilks test, $p = 0.28$). Agreement between both assessors is shown in figure 3. The interclass correlation coefficient, which replaces the kappa index for continuous variables, used to assess agreement between independent assessors was 0.96 (95%CI 0.92-0.98).

DISCUSSION

The rating scale specifically designed to assess studied comparing hemodialysis techniques has shown to be an accurate and reproducible tool. The agreement reached between both reviewers has been high and those considered as having the highest quality have rated with the best scores, as has been the case with the HEMO study.

The *U.S. Preventive Services Task Force* rating scale, one of the most frequently used, forces the inclusion of a study in a determined category, with no consideration other than its design. This rigid classification also occurs with other scales.[6,7] In the particular case of the present review, selection criteria condition study inclusion in only categories I, II-1, and II-2, concluding on the existence of an adequate or true evidence to recommend the use of a particular technology. Other commonly used scales,[45-47] rate the different evidence levels by cer-

tain study characteristics such as random assignment to the experimental and control groups, the existence of a concomitant control group, patients randomization, and sample size, but do not take into account other essential issues that involve assessment and comparison of efficacy of different dialysis modalities.

Within a same dialysis modality, there are many factors that may vary and affect its efficacy, such membrane type, dialysate quality, dialysis duration, or dialysis dose. The quality rating scale built for this report does not only assess design characteristics, but also takes into account the technique characteristics and many other issues that limit the validity of the studies and the outcomes inference capability. For instance, the dialytic age of patients and presence of comorbidities are taken into account, data that would not be possible to consider when using other scales and that bring information on the capability of applying the obtained results to other settings or populations (external validity).

Regarding the scores of the scale itself, in particular the general study characteristics, the item receiving the higher score (up to 15%) was the type of design, and this maximal value was assigned to randomized clinical trials, which makes sense since they provide the greater degree of evidence. The lowest score was assigned to retrospective cohort studies, since this type of design is subjected to a higher bias rate, the observer being placed at a point of time when exposure and effect have already occurred. Sample size did not receive as much importance as the study design, so the studies including 100 patients were assigned a maximum value of 12.5, since it was considered that number was big enough to obtain more or less accurate estimates and that chance would have less influence on sample of that size. The follow-up time was assigned a 12.5% value, assigning this score to studies with more than one year of follow-up. The occurrence and severity of clinical impairments is a process that runs parallel to renal damage progression. In appropriately treated and controlled patients, this process slows down and a prolonged follow-up time would be necessary to assess how the different dialysis modalities influence their onset.

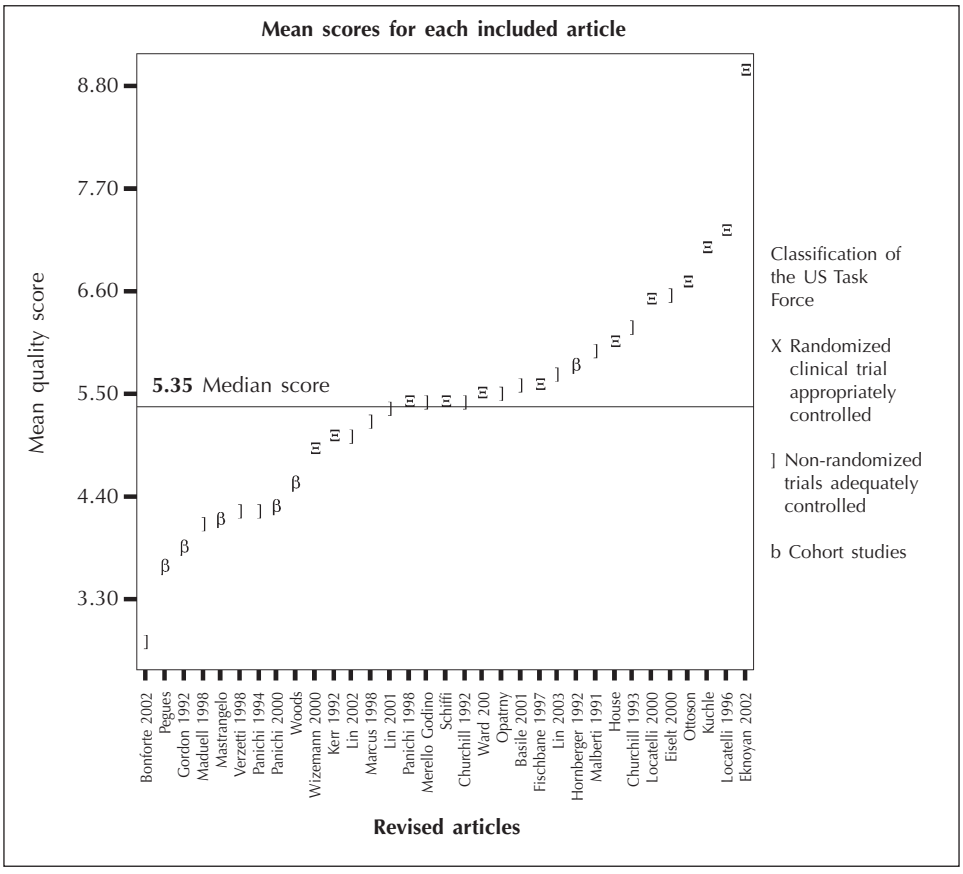

Fig. 2.—Quality assessment of included studies.

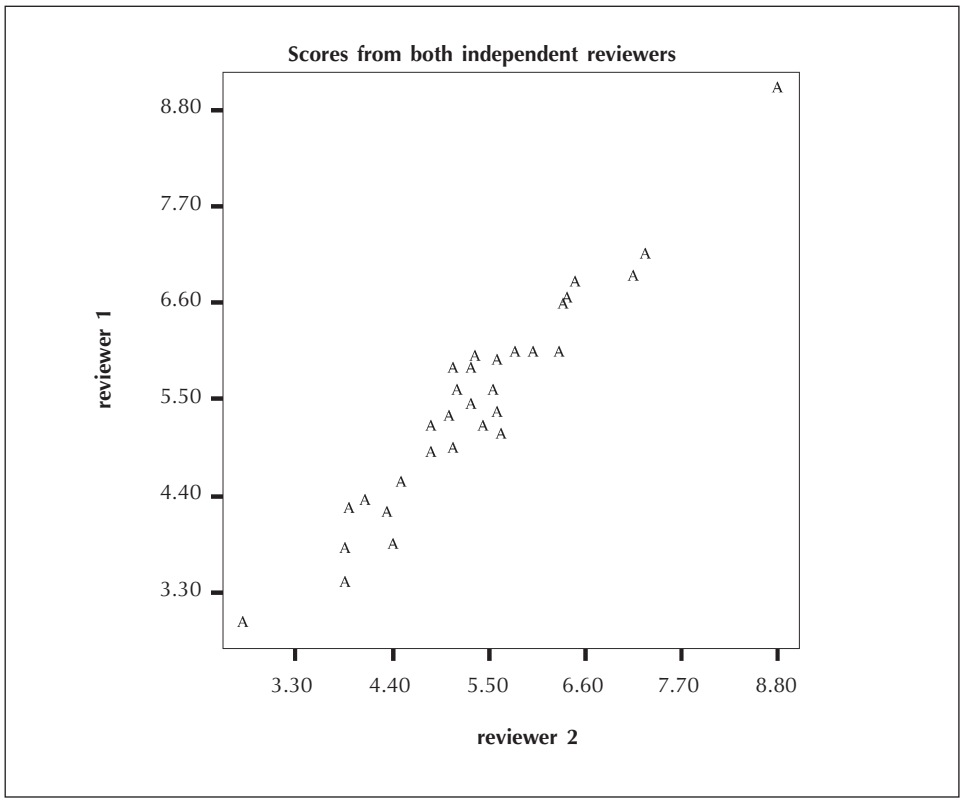

Fig. 3.—Agreement between both reviewers.

The specific study characteristics received lower scores than general ones since they refer to particular design issues that, although they may influence the outcome, it is not in the same way as, for instance, follow-up time or sample size. For clinical trials, two items received the maximum score, the existence of concurrent controls and the existence of losses to follow-up (being differential) greater than 20%. The absence of non-concurrent controls limits groups comparability as regard to other factors (treatments received, dialysis membranes usage, etc.). Losses to follow-up mean lack of adherence and if they are differential between groups they may be masking a different effect with any of the dialysis modalities.

Other items taken into account were knowledge of the randomization or assignment methods, appropriate description of the study population, and results interpretation, as well as the definition of inclusion and exclusion criteria. Groups comparability was also checked for confounding factors and the existence or absence of blinding since it has been done in some studies, although it is difficult to perform. The comparability between groups of follow-up times was also assessed in order to allow enough time for the occurrence of some sort of event with dialysis modalities being compared, and also whether that event had been assessed in the same in both groups.

The assessment of cohort studies consisted on 7 items, given a score of 7-3%. The maximum score was for groups comparability by disease status (an essential issue in this type of design) and by presence of possible confounding factors for CRF.

The section pertaining to patients' characteristics was assigned 20% of the whole scale, and comprised two items. The first one, years on dialysis, valued as 15%. This is an important issue in hemodialysis studies since the accumulation of toxic substances increases with time, having an effect on quality of life of hemodialyzed patients and possibly on the efficacy of a new modality being evaluated. The ideal would be studies recruiting incident patients, i.e., starting from a same renal function status and on which no previous dialysis modality may have had an influence.[48] The other item was the presence of comorbidities. This factor could reach a score up to 5% with the absence of any comorbidity in more than 50% of included patients. The rationale for including this parameter in the quality scale is that the existence of comorbi-

dities may affect the outcomes of the dialysis modality being studied. If a considerable number of study subjects present, for instance, diabetes, hypertension, or coronary heart disease, and are put together with patients not having other diseases, is may be difficult to know whether the results may be attributes to the dialysis modality itself or to the existence of those factors that may modify the effect.

This quality scale presents limitations, perhaps the main one being the fact that it has been created in a way that the scores assigned to each item have been obtained by consensus. We have try, however, to quantify by the more appropriate way each one of the issues implicated in the validity (internal and external) of this type of studies. Thus, 80% is the internal validity weight (general and specific characteristics) and 20% represents the external validity. It should be reminded that a study has to have first internal validity in order to have external validity. Another limitation that we believe the scale may have is that it may be that the number of items for each study type may be high or difficult to apply by professionals with insufficient epidemiological knowledge; however, the answers to each item ought to be given in the article so that, in theory, the scale should not be difficult to apply. In case of lack of information, the assessed item should be given the lowest value.

To conclude, we believe that there is a relatively large volume of literature concerning the different hemodialysis techniques, but without adequate judgment elements that allow classifying the literature quality, which is occasionally leading to the use of hemodialysis modalities with no clear-cut criteria in many cases. We would like to encourage the use of (and critic) the proposed scale, or an adaptation, by professionals (and also reviewers) to objectively assess the quality of new studies. This will allow us to have a clue on the quality of the evidence is being published.

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