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Methodological Quality of Studies of End-stage Renal Disease in Lupus Nephritis, 1970 to 2015

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Abstract

Objective—To examine trends in methodological quality of studies of end-stage renal disease risk in lupus nephritis, 1970–2015.

Methods—We assessed quality using the Newcastle-Ottawa scale for observational studies, and Cochrane Collaboration’s risk of bias tool for trials.

Results—In observational studies, description of enrollment criteria was high but decreased over time. Adequacy of follow-up was low but improved. Inception cohorts and community-based studies were uncommon. Trials had low risk of bias in blinding and selective outcome reporting but most had unclear risks in sequence generation and allocation concealment.

Conclusion—Methodological quality was mixed, with limited improvement over time.

Key indexing terms

lupus nephritis; end stage renal disease; methodological quality; observational studies; clinical trials

Introduction

End-stage renal disease (ESRD) is a severe potential complication of systemic lupus erythematosus. To examine whether the risk of ESRD changed over time, we recently performed a systematic review and meta-analysis of all published studies up to April 2015 that reported the risk of ESRD in lupus nephritis [1]. We observed that risks of ESRD improved between the 1970’s and the mid-1990’s, and then plateaued, with an increase in the 2000’s.

Assessing methodological quality of clinical studies is important for proper interpretation of their findings [2]. With the maturation of clinical epidemiology since the 1980's and the development of reporting guidelines, such as the CONSORT statement for clinical trials [3] and the STROBE statement for observational studies [4], both the design and reporting of clinical studies would be anticipated to have improved over time. Several tools have been proposed for assessing study quality. In 2008, the Cochrane Collaboration introduced a tool for assessing the risk of bias in clinical trials [5]. Wells et al proposed the Newcastle-Ottawa scale for assessing the quality of nonrandomized studies in meta-analyses [6].

The purpose of this study was to determine trends in methodological quality of studies of risk of ESRD in lupus nephritis since 1970.

Methods

In our systematic review, we searched PubMed, Embase, and the Cochrane Database of Systematic Reviews from their inception to April 7, 2015 for studies on the risk of ESRD in adults with lupus nephritis [1]. We included 187 studies; 144 observational studies and 43 clinical trials (Supplement). The study was exempted from ethics review by the NIH Office of Humans Subjects Research Protection because it was designated as not human subjects research.

Methodological quality assessment was independently performed by each author using a protocol. Discrepancies were resolved by discussion. For observational studies, we assessed methodological quality using ten items in three domains, adapted from the Newcastle-Ottawa scale: completeness of description of enrollment criteria and treatment; adequacy of follow-up; and representativeness of the cohort (Table 1). In this analysis, we omitted two items (related to renal biopsy and patients with chronic kidney disease) because they are not generalizable measures of quality applicable to studies of nephritis outcomes. Each item was rated as present or absent.

For clinical trials, we used the Cochrane Collaboration's tool [5] to assess the risk of bias in five domains (Table 1): sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; incomplete outcome data; selective outcome reporting. In each domain, the risk of bias was graded as high (plausible bias that seriously weakens confidence in the results), uncertain (plausible bias that raises some doubt about the results), or low (plausible bias unlikely to seriously alter the results).

We classified studies by their decade of publication (pre-1990, 1990 – 1999, 2000 – 2009, and 2010 and later) and computed the proportion of studies in each decade that satisfied each quality measure. For observational studies, we used logistic regression analysis to compare these proportions by examining linear trends in odds ratios across decades. Because large studies and studies from developed countries may have different designs than small studies and those from developing countries, we adjusted these analyses for study size (less than 100 patients versus 100 or more patients) and developed versus developing country of origin. Development status of the study's country of origin was based on the World Bank's

rating [7]. For trials, we compared trends across decades using Chi-square tests. There were too few trials to support multivariate analysis.

For both sets of studies, we also examined trends using publication year as a continuous variable in logistic regression models, and tested whether quality reporting differed after publication of the STROBE and CONSORT statements.

We used SAS programs, version 9.3 (SAS Institute, Cary, NC) for analyses.

Results

Observational Studies

Twelve studies were published before 1990, 36 studies were from 1990–1999, 55 studies were from 2000–2009, and 41 studies were published in 2010 or later. Overall, 38% were from developing countries, and 32% were large studies. The proportion of observational studies from developing countries increased from 17% in the pre-1990 period to 46% in 2010 and later. The proportion of large studies also increased, from 8% to 39%, over this time, with large studies evenly reported from developed countries and developing countries (50% each).

Description of enrollment criteria was high, but decreased from 92% before 1990 to 78% in 2010-present ($p = 0.04$) (Figure 1). The adjusted odds ratios for reporting of enrollment criteria, with pre-1990 as the reference group, were 0.82 (0.08, 8.82) for 1990–1999, 0.27 (0.03, 2.38) for 2000–2009, and 0.23 (0.02, 2.06) for 2010 and later. Reporting on renal function and treatment at study entry was high and stable over time.

The proportion of studies of inception cohorts ranged from 33% to 43% and did not change over time ($p = 0.43$). Notably, in studies from developing countries this proportion increased from 0% before 1990 to 40% in 2010-present. The proportion of studies with community-based enrollment remained very low.

The proportion of studies reporting on losses to follow-up was low but improved across decades. The proportion that described the nature of losses increased over time ($p = 0.05$), with an adjusted odds ratio for reporting on losses to follow-up in 2010 and later of 5.15 (0.57, 46.21), compared to pre-1990. Similarly, the adjusted odds ratio for a study having less than 20% loss to follow-up in 2010 and later was 3.54 (0.65, 19.11), compared to pre-1990 ($p = 0.06$). There was no appreciable increase in the proportion of studies reporting results with Kaplan-Meier plots. Seventy percent of recent studies did not use the Kaplan-Meier method to assess the time to ESRD.

The median number of criteria (of eight) met per study in studies from developing countries increased over time (2.5, 3, 3, and 4 in pre-1990, 1990–1999, 2000–2009, and 2010 or later, respectively), but did not increase in studies from developed countries (3.5, 4, 3.5, 4 in each decade, respectively).

Using publication year as a continuous variable, only the likelihood of reporting renal function increased over time (Supplemental table 1). There was no change in likelihood of quality measures being included after the STROBE statement in 2007 (all $p > 0.15$).

Clinical Trials

Six trials were published before 1990, ten trials were from 1990–1999, fifteen trials were from 2000–2009, and twelve trials were published in 2010 or later. Most trials had an unclear risk of bias for sequence generation and allocation concealment, increasing to 80% and 92%, respectively, during the last decade (Figure 2). This principally was the result of incomplete description of the methods of randomization. All trials were rated as having low risk of bias in the domains of blinding and selective outcome reporting. Although most trials were not blinded, the objective nature of the outcomes, including primarily laboratory measures and ESRD or death, afforded a low likelihood of bias. Additionally, 80–90% of trials had a low risk of bias for incomplete data on outcomes, with no trend across decades. The median number of criteria (out of five) with low risk of bias per study was three in each decade. There were no trends across calendar years of publication (Supplemental table 2), and no change after the CONSORT statement in 1996 (all $p > 0.65$).

Discussion

Among observational studies of ESRD risks in lupus nephritis, at least half of the methodological quality criteria were uncommonly met. Only two criteria, both related to losses to follow-up, improved significantly over time. The quality of observational studies from developing countries improved over time, coming to match those from developed countries in number of criteria satisfied in recent years. Among trials, blinding, outcome reporting, and completeness of outcomes had low risk of bias, while incomplete descriptions of the randomization process lead to unclear risks of bias for these criteria.

Several factors may account for these findings. Lack of appreciation of the study design features that are important for ensuring high methodological quality may cause investigators to omit implementation of these characteristics or omit them in study reports [8–10]. Reporting is essential to ensure that high quality studies are recognized. Some decisions that occur at the study design stage, particularly the choice to enroll a community-based or inception cohort or not, are often predicated on feasibility [10]. Even though such studies are more difficult to conduct, their enhanced validity should encourage greater use.

Several key design features should be included in all outcome studies. Enrollment criteria, patient characteristics, and treatment should be reported. Kaplan-Meier curves should be used to present time-to-event data [14]. Also, data on the adequacy of follow-up, including the proportion and reasons for losses to follow-up, should be reported [13, 14]. Inception cohorts should be studied whenever possible. In trials, the process of random allocation sequence and adequate allocation concealment should be reported to allow assessment of possible selection bias [15, 16].

While many studies of outcomes in lupus nephritis fulfill several quality criteria, there is room for improvement. Researchers can improve the quality of the literature by considering

these features in both the design and reporting of studies. Readers should also consider how the presence or absence of these features impacts their appraisal of a study's findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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a

b

Figure 1.

- a. Proportion of observational studies that met study quality criteria by decade of publication
- a. description of ACR criteria, renal function characteristics, and treatment
- b. Proportion of observational studies that met study quality criteria by decade of publication
- b. community-based and inception cohorts
- c. Proportion of observational studies that met study quality criteria by decade of publication
- c. Kaplan-Meier methods and loss to follow-up

Figure 2. Risk of bias in five domains among clinical trials, by decade of publication a. Sequence generation; b. Allocation concealment; c. Blinding ; d. Incomplete Outcome data; e. Selective outcome reporting

Table 1

Methodological quality criteria in observational studies and clinical trials.

Observational Studies	Rationale
A. Completeness of Patient Descriptions	
1. Were American College of Rheumatology classification criteria for SLE and lupus nephritis used for enrollment?	Description of the American College of Rheumatology classification criteria for SLE and lupus nephritis allows standardization of patient inclusion and appraisal of the accuracy of diagnosis
2. Were measures of renal function at study entry provided?	Description of the patient characteristics is important for determining representativeness and possible selection bias
3. Were data on treatment provided?	Description of medication use is important for determining its potential effect on the outcomes
B. Representativeness	
4. Was an inception cohort studied?	In inception cohorts, patients are identified at an early and uniform point in the course of their disease, minimizing bias that may occur by omitting patients who meet the study outcome shortly after diagnosis.
5. Was the cohort community-based?	Recruiting community-based samples of patients can help to achieve greater representativeness compared to cohorts based at referral centers
C. Adequacy of Follow-up	
6. Were losses to follow-up reported?	Loss to follow-up can affect the validity of study since patients lost to follow-up may have different outcomes than those who complete the study
7. Were losses to follow-up less than 20%?	Loss to follow-up of more than 20% of patients can seriously affect the validity of results because variant outcomes in this subset are often large enough to affect the overall study estimate
8. Were time-to-event data provided as Kaplan-Meier plots?	Kaplan-Meier plots provide a complete history of events in the study and is the standard method to present time-to-event data
Clinical trials	Rationale
1. Sequence generation (methods of random assignment to intervention groups)	Random assignment of patients can ensure equivalent-group comparison, eliminating selection and confounding biases
2. Allocation concealment (methods of concealing the allocation sequence from those enrolling patients)	Allocation concealment prevents selection bias
3. Blinding of participants, personnel and outcome assessors (a practice of keeping patients and personnel unaware of which intervention is administered to which participant. In cases of no blinding, the likelihood that open-label treatment could influence the outcomes should be low.)	Blinding is important because knowledge of which group the patient has been assigned to may affect the outcome
4. Incomplete outcome data (missing data due to attrition or due to exclusion from the analysis)	Missing data may introduce bias if the number and characteristics of people lost to follow-up differ between the groups
5. Selective outcome reporting (information about whether outcome reporting is sufficiently complete and transparent)	Reporting of some outcomes but not others introduces bias