Risk factors associated with mortality in systemic lupus erythematosus. A case-control study in a tertiary care center in Mexico City

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Abstract

Objective

To identify the mortality risk factors in a group of Mexican patients with SLE.

Methods

A case-control autopsy study in a tertiary care center in Mexico, City. Patients with SLE who died during 1958 to 1994 with an autopsy study were selected as cases, and alive patients matched by age (±3 years), decade of SLE onset, and disease duration (±5 years) were defined as controls. Clinical charts were reviewed looking at clinical variables. SLE disease activity was evaluated with the MexSledai index, and SLE disease severity with the Severity Index. Variables were classified as present at any moment during the follow-up and 3 months before death in cases or cut-off date in controls. Statistical analysis: matched univariate and multivariate analysis by multiple logistic regression were performed, and the results were presented as odds ratio and 95% confidence intervals (OR, 95%CI).

Results

76 matched pairs of patients were studied. Age, gender, and years of formal education were similar in the cases and controls. Variables associated with mortality three months before death were: lung involvement OR=15.6, 95%CI (4.8-50.3), p<0.001; severe thrombocytopenia 9.6 (2.9-31.7), p<0.001; heart involvement 5.8 (2.6-13.0), p<0.001; and the severity index (cases 8.8 , 2.4 vs controls 3.5, 2.0, respectively) 2.2 (1.5-3.4), p<0.001. Variables associated with mortality detected at any moment before death were kidney involvement 2.16 (1.09-4.29), p<0.02; the steroid therapeutic index 2.3 (1.2-4.5), p<0.001; number of previous admissions 2.4 (1.4-4.3), p<0.001; the MEX-SLEDAI index (cases 21.6 , 6.3 vs controls 12.6, 5.8), 1.2 (1.1-1.3), p<0.001; and the number of severe infections 14.4 (4.4-46.2), p<0.001. Protective variables were skin involvement 0.1 (0.3-0.6), p<0.001; daily dose of chloroquine (cases 3.9 , 24.1 vs controls 39.4, 60.0 mg), p <0.0001 and the time from the first SLE symptom to the patient's demise or the cut-off date 0.7(0.6-0.9), p<0.001. Multiple logistic regression showed that the model which best explained mortality consisted of a severity index 2.6 (1.7-3.8), p<0.001; heart disease 6.5 (1.5-28.2), p=0.01, and steroid therapeutic index 3.3 (1.6-6.6), p=0.001.

Conclusions

An active SLE with multi-organic involvement, steroids and infections were associated with mortality in Mexican patients with lupus attended in a tertiary care center. A protective effect of cutaneous disease and chloroquine use was observed.

Key words

Systemic lupus erythematosus, mortality, autopsy study, disease activity.

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Received on August 16, 2000; accepted in revised form on February 7, 2001.

Introduction

Survival in systemic lupus erythematosus (SLE) has been improving during the last 50 years (1,2). In 1954 the five-year survival rate was less than 50% (3), while in 1993 it ranged between 89% (4) and 93% (5). The ten-year survival figures approach 70% (6), but with lower figures in SLE patients from developing countries (6-8).

Race, gender, old age at onset, thrombocytopenia, nephritis, central nervous system involvement,and disease activity are risk factors associated with mortality in patients with SLE (1-10). However, these causes have changed, and a bimodal mortality pattern has been described (5, 6, 11-13).

Causes of death in SLE patients have been divided into: (i) those directly related to SLE, either active SLE (i.e., central nervous system, kidney, or heart involvement) or sequelae of the disease; (ii) those related to immunosuppressive therapy (basically severe or opportunistic infections, and probably cardiovascular disease), and (iii) deaths from unrelated causes (1-5, 14, 15).

In this paper we analyzed the risk factors associated with mortality and the main related causes of death in a group of Mexican patients with SLE. A case-control study was used with a set of autopsies from adults with SLE, performed during 1958 to 1994 in a tertiary care center in Mexico City.

Patients and methods

Cases were in-patients with SLE (16) who died from 1960 to 1994 and had an autopsy study. Cases were selected from the autopsy registers from the Pathology Department. Controls were alive in-patients with SLE (16). Controls were alive at time of the case's death, and the follow-up of each control was until the death date of the matched case ±5 years. Controls were randomly selected from the database of in-patients with SLE. Cases and controls were matched by age (±3 years), decade of SLE onset, and disease duration (±5 years).

This group of patients was collected from 1958 to 1994 and did not represent all patients with SLE who died in our institution. This may imply a selection bias, in that only patients with a postmortem study were included. However, the causes of death of patients in this study and of patients in our SLE cohort, in which the 10-year survival rate was 82% (10), were similar.

From clinical charts the same investigator (NT) looked for the following variables:

Demographic variables: Age and gender.

SLE-related variables: Disease duration: (i) from first SLE symptom, (ii) from the moment when the patient met 4 SLE criteria, and (iii) from the first time attending our hospital to the patient's decease or the cut-off date

Clinical signs and symptoms:

Lung involvement was defined as the presence of: 1. Pleuritis (typical pain and/or pleural rub, and pleural effusion evidence by chest x-ray, ultrasonography or other image study, after excluding other causes). 2. Pulmonary hemorrhage (hemoptysis or dyspnea, serum hemoglobin level reduction of >1 g/dl, and a suggestive bronchoalveolar lavage or lung biopsy. 3. Pneumonitis (cough and dyspnea and bronchoalveolar lavage or pulmonary biopsy with evidence of inflammation). 4. Arterial pulmonary hypertension (clinical data plus pulmonary capillary wedge pressure > 40 mmHg).

Severe thrombocytopenia: a platelet count < 50,000 mm^3.

Heart involvement: 1. Pericarditis (pain or pericardial rub and pericardic effusion demonstrated by chest x-ray or echocardiography).2.Myocarditis (persistent tachycardia, or arrhythmia or cardiac failure and echocardiograph findings after excluding other diseases). 3. Libman-Sachs endocarditis by echocardiography.

SLE nephritis according to the WHO classification (17).

Severe infections: Infections, which required hospitalization for their diagnosis and/or treatment.

Presence of secondary antiphospholipid syndrome (18).

Activity index (MexSledai) (19). The MexSledai is a modified version of the SLEDAI index. In this short form, the original 24 items are reduced to 10 main clinically defined variables (19).

Variables are grouped by target organ and they are scored in this way: neurologic disorder (score = 8), renal disorder (score = 6), vasculitis (score = 4), haemolysis and/or thrombocytopenia (score = 3), myositis (score = 3), arthritis (score = 2), mucocutaneous disorder (score = 2), serositis (score = 2), fever and/or fatigue (score = 1), and leukopenia and/or lymphopenia (score = 1). The total score ranges are from 0 points (which means SLE in remission) to 32 (which means the highest level of disease activity). The evaluation was made in the last 90 days before the death or cut-off date, and did not include the terminal event.

Persistent activity was defined as a MexSledai >2 in the last 3 months before death. In controls a similar MexSledai Index was measured until the cut-off date was scored.

Severity index (20). This is a cumulative index. It includes 10 items with different scores. The following four items each receive one point: the lowest recorded hematocrit to date = 30-37%; history of proteinuria (2+ or more); higher recorded creatinine to date = 1.3 to 3 g/dl; 4-6 ACR criteria for SLE satisfied to date. The following six items each receive two points: history of cerebritis (seizure or organic brain syndrome); history of pulmonary disease (lupus pneumonitis, pulmonary hemorrhage or pulmonary hypertension; lowest recorded hematocrit to date <30%; highest recorded creatinine >3; biopsy proven diffuse proliferative glomerulonephritis; seven or more ACR criteria for SLE satisfied to date. The index score may be from 0 for less severity to 13 for the higher severity. The severity index was validated. It showed face and construct validity, reliability and feasibility in two SLE populations (20). The evaluation was made in the last 90 days before the death or cut-off date, and did not include the terminal event.

Number of admissions.

SLE treatment: mean daily dose, total dose and duration of steroids, chloroquine, azathioprine, methotrexate, and/or cyclophosphamide treatment. When methylprednisolone pulses were administered, the dose was changed to a prednisone equivalent. A steroid therapeutic index was constructed with the addition of each daily dose (the cumulated daily dose) ∏ (the number of days on treatment).

Comorbidity: presence of hypertension, diabetes mellitus, obesity, nephrotic syndrome, and severe infections.

Variables were classified as present at any moment during the evolution of SLE or 3 months before death (cases) or the cut-off date (controls).

Autopsy study. The autopsy study was either complete or restricted to thoracic, abdominal, retroperitoneal, and pelvic organ examination (21). The final histopathological diagnosis was used as a gold standard to define the main cause of death. In our hospital, autopsies are requested on all deaths and are carried out only with the relatives' written approval.

Statistical analysis

The first step of the analysis was performed with matched contingency tables. Odds ratios and 95% confidence intervals were calculated. Comparison of continuous variables was done with the paired Student's t-test or Mann-Whitney's U test, as appropriate.

Matched logistic regression was performed in order to evaluate the independent participation of the variable that were significant in the crude analysis, with biologic sense. In this analysis, the dependent variable was death, and the independent variables were the severity index, MexSledai index and the rest of the possible variables not included in the index with p values < 0.2. Variables included in the indexes were excluded from the model, and models with variables not associated with the indexes also were constructed. We also did matched multiple conditional logistic regression. The results with both methods were similar. Significance was set at the two-tailed 0.05 level.

Results

During the analyzed period we identifued 104 patients with SLE and autopsy study. Of these, 76 patients were selected as cases. Twenty-eight (27%) autopsies were excluded because of incomplete or lost clinical charts (n=12, 11.5%) or inadequate matching (n=16, 15%).

The mean age for all patients was 28.5 (range 13-68) years, with a male: female ratio of 1:37. Patient's age, gender, and years of formal education did not show differences between cases and controls. Disease duration from the first SLE manifestation to death or the cut-off date was 4.0, 5.7 (range 0.1-45 years in cases) and 5.7, 5.3 (range 0.2-34 years) in controls, p=0.07 (Table I).

Causes of mortality are shown in Figure 1. Infection was the main cause of

Table I. Main characteristics of cases and controls.

Variable	Cases (n = 76) , range	Controls (n = 76) , range	Cases and controls (n = 152) , range	P
Age of admission (years)	28.1, 10.9, 13-68	28.3, 10.6, 13-64	28.5, 10.7, 13-68	0.8
Formal education	9.2, 6, 0-18	9.9, 5, 5-16	9.1, 3.4, 3-18	0.5
Time of SLE, from first symptom to death or cut off date (years)	4.0, 5.7, 0-45	5.7, 5.3, 0-34	4.8, 5.6, 0-45	0.07
Disease duration from diagnosis to death or cut off date (years)	1.8, 2.9, 0-16	3.5, 3.8, 0-20	2.7, 3.5, 0-20	0.002

= mean; = standard deviation.

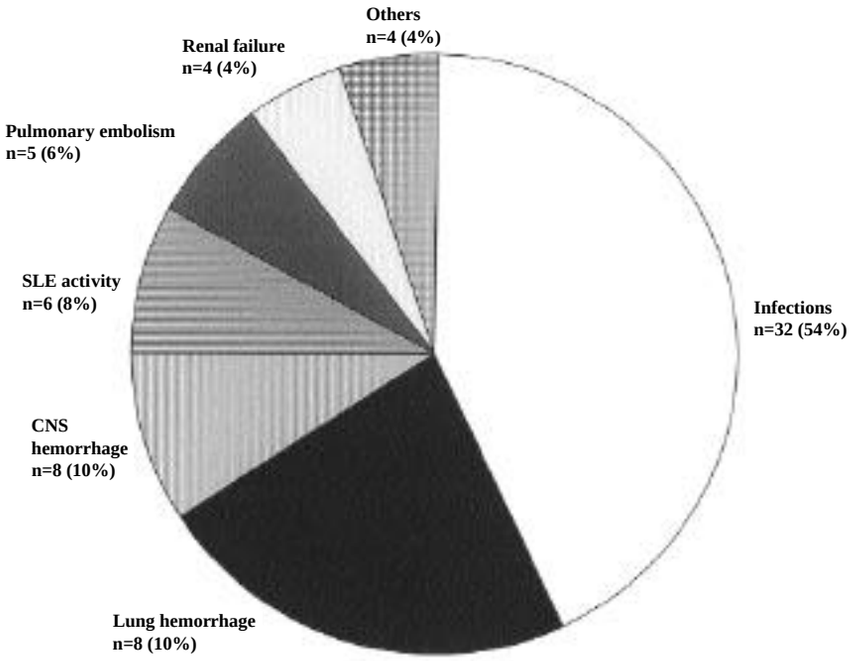

Fig. 1. Causes of mortality in the patient series.

Table II. Causes of mortality by decade of death in 76 cases with SLE.

Cause of death	Decade of death				
	1960 n (%)	1970 n (%)	1980 n (%)	1990 n (%)	Total n (%)
Infections	3 (4)	8 (10)	15 (20)	6 (8)	32 (41)
Lung hemorrhage	5 (7)	5 (7)	5 (7)	2 (3)	17 (24)
Central nervous system hemorrhage	3 (4)	2 (3)	2 (3)	1 (1)	8 (11)
SLE activity	0	1 (1)	4 (5)	1 (1)	6 (7)
Pulmonary embolism	0	1 (1)	2 (3)	2 (3)	5 (7)
Renal failure	3 (4)	1 (1)	0	0	4 (5)
Myocardial infarction	0	0	2 (3)	0	2 (3)
Acute pancreatitis	0	1 (1)	0	0	1 (1)
Liver failure	0	0	1 (1)	0	1 (1)
Total	14 (19)	19 (24)	31 (41)	12 (16)	76 (100)

Table III. Causes of mortality by disease duration (from the first SLE symptom to death).

Cause of death	SLE duration in years			
	0-4.9 n (%)	5-9.9 n (%)	10 or more n (%)	Total n (%)
Infections	26 (34)	3 (4)	3 (4)	32 (41)
Lung hemorrhage	11 (14)	4 (5)	2 (3)	17 (24)
Central nervous system hemorrhage	7 (9)	1 (1)	0	8 11)
SLE activity	3 (4)	2 (3)	1 (1)	6 (7)
Pulmonary embolism	3 (4)	1 (1)	1 (1)	5 (7)
Renal failure	3 (4)	1 (1)	0	4 (5)
Myocardial Infarction	0	0	2 (3)	2 (3)
Acute pancreatitis	0	1 (1)	0	1 (1)
Liver failure	0	1 (1)	0	1 (1)
Total	53 (70)	14 (18)	9 (12)	76 (100)

mortality. There were 16 cases with bacteremia or septicemia; in these cases, the affecting microorganisms were: *Escherichia coli* (n=3), *Pseudomona sp* (n=2), *Staphylocossus aureus* (n=2), *Klebsiella pneumoniae* (n=2), *Candida sp* (n=2), and one each for *Criptococ - cus neoformans*, *Enterobacter sp*, *As - pergillus sp*, Nocardia and Mucormicosis. Eleven cases had pneumonia by *Streptococcus pneumoniae* (n=2), *Es - cherichia coli* (n=2), *Pseudomona aeu - riginosa* (n=2), *Staphylococcus aureus*, *Mycobacterium tuberculosis*, *Aspergil - lus sp*, *Pneumocystis carinii*, and *Cyto - megalovirus* (n=1). There were 3 cases with meningitis by *Criptococcus neo - formans*, *Lysteria monocytogenes* and *Staphylococcus aureus*, and 2 with *Sta - phylococcus aureus* endocarditis.

All cases with pulmonary hemorrhage had active SLE with a MexSledai index > 2. Central nervous system hemorrhage was due to severe thrombocytopenia associated to SLE activity. Patients with SLE activity as the cause of death had severe multi-organ involvement with central nervous system damage, proliferative diffuse glomerulonephritis, and/or heart failure due to myocarditis. Pulmonary embolism was an autopsy finding in 5 patients. Four patients died of renal failure and these deaths occurred before 1975. Other causes of death included 2 patients with myocardial infarction and 2 with acute pancreatitis or hepatic failure (Table II).

The most frequent causes of death for patients in the first 5 years of SLE were infections and lung hemorrhage followed by SLE multi-organ involvement, while between the 6th and 10th years of disease the mortality causes were infection, pulmonary embolism, and disease activity. In contrast, after a disease duration of 10 years the main causes of mortality were infections, activity, and cardiovascular diseases (Table III).

Variables associated with mortality present in the last three months before death or the cut-off date are shown in Table IV. These variables were lung involvement, severe thrombocytopenia, and heart involvement.

In the cases the mean severity index

Table IV. Variables associated with mortality present in the last 3 months before death or cut off date in cases and controls.

Variable	Cases (n=76)	Controls (n=76)	OR (95% CI)	p value
Lung involvement	60 (78%)	20 (21%)	15.6, 4.8-50.3	< 0.001
Severe thromocytopenia	31 (41%)	4 (5%)	9.6, 2.9-31.7	< 0.001
Heart involvement	49 (64%)	14 (18%)	5.8, 2.6-13.6	< 0.001
Severity index ( )	8.8, 2.4	3.5, 2	2.2, 1.5-3.4	< 0.001

= mean. = standard deviation.

Table V. Variables associated with mortality present at any moment before death or cut off date in cases and controls.

Variable	Cases	Controls	OR, 95% CI	P value
Nephritis	46 (60%)	32 (42%)	2.1, 1.09-4.2	0.02
Steroid therapeutic index	88.8	20.4	2.3, 1.2-4.5	<0.001
MexSledai ( )	21.6, 6.3	12.6, 5.8	1.2, 1.1-1.3	<0.001
Number of admissions			2.4 (1.4-4.3)	<0.001
1	42 (55%)	66 (87%)		
2	15 (20%)	6 (8%)		
3	10 (13%)	1 (1%)		
4	4 (5%)	1 (1%)		
5	2 (3%)	1 (1%)		
6	3 (4%)	1 (1%)		
Number of severe infections			14.4 (4.4-46.2)	<0.001
0	23 (30%)	63 (83%)		
1	37 (49%)	9 (12%)		
2	10 (13%)	3 (4%)		
3	6 (8%)	1 (1%)		
Skin involvement	60 (79%)	72(95%)	0.1, 0.3-0.6	<0.001
Dose of chloroquine mg/day ( )	3.9, 24.1	39.4, 60		<0.001

= mean; = standard deviation.

Table VI. Multiple logistic regression model.

Variable	OR, 95% CI	p
Heart disease	6.5, 1.5-28.2	0.01
Severity index	2.6, 1.7-3.8	<0.001
Steroid therapeutic index	3.3, 1.6-6.6	<0.001

score was 2.5 higher than in controls. There was a direct correlation between the severity index score and the patient status. Thus, all patients with a severity index score ≤ 3 were alive and none of the patients with a score ≥10. For each additional point in the severity index, the probability of death rose by 20% (95% CI 50%-240%).

Variables associated with mortality present at any time before death or the cut-off date are shown in Table V. These variables were nephritis, the steroid therapeutic index, MexSledai and severe infections. The mean MexSledai index was 1.7 higher in cases than in controls, and patients with a MexSledai score ≤ 6 were alive, in contrast to patients with a MexSledai score ≥30. A MexSledai index >2 was present in all cases and in only 25% of the controls. The probability of death increased by 20% (10-30%) for each point increase in the MexSledai index score.

Persistent disease activity in the last 3 months before death was observed in 80% of the patients who died, while it was observed in only 13% of the controls. In contrast, the probability of death increased by 1,340% (340%-4,520%) with each severe infection, and by 140% (40%-330%) with each previous admission to the hospital.

Protective variables were skin involvement and treatment with chloroquine.

In the matched multiple logistic regression analysis, the model which best explained mortality was composed of heart involvement, the severity index and the steroid therapeutic index (Table VI).

Discussion

Our autopsy based case-control study included 76 patients with SLE plus a postmortem study (cases) and 76 matched living patients with SLE (controls). Regarding the risk factors associated with mortality, we found that the patients who died had a shorter disease duration but with the characteristic of having a delayed diagnosis. It must be remembered that a late diagnosis has been a clinical factor associated with a poor prognosis (7-10,22). The age of the patients was not analyzed because it was a matching variable, in order to minimize heterogeneity problems. This also applies to the decade of SLE onset. Gender was not a risk variable, perhaps due to the low proportion of men in our study. The results of different variables present three months before death showed that the most common variables related to a worse prognosis were lung involvement, mainly severe pulmonary hemorrhage and lung hypertension. Lung involvement was previously reported as a risk factor associated with mortality in the Toronto series of SLE patients (5). In recent series, the reported frequency of mortality due to pulmonary hemorrhage was 50% to 72% (23, 24) and the frequency due to pulmonary hypertension was between 30% to 70% (25). Severe thrombocytopenia is an accepted death-related variable by several authors (1,5,8), as well

as in a subset of patients with antiphospholipid syndrome and SLE at our hospital (10).

Information on the predictive value of activity and severity as markers of mortality in SLE is scarce. In our study we found a strong association between the activity and severity indexes, with higher scores of activity (19) and severity (20) in both cases and controls. Abu-Shakra *et al.* reported that patients with higher activity at presentation to clinic had a higher mortality rate (5), and a recent paper shows that patients with a SLEDAI score > 20 face over 14 times the risk of death in the next months than subjects with a SLEDAI score of zero (26). The severity index parameters hematocrit, proteinuria, serum creatinine, number of SLE criteria, central nervous system damage, lung involvement, and proliferative diffuse glomerulonephritis were closely associated to mortality. To our knowledge there are no reports using this index as a predictor of mortality. In the past, it was described that activity and severity were not synonymous in SLE, but they have a close relationship (27). This concept was also applied to chronicity indexes (28).

Regarding the variables present at any moment during the disease, nephritis, steroid therapeutic index, activity index, infections and previous admissions were markers of both activity and comorbidity. Multiple logistic regression analysis disclosed that the variables of activity and comorbidity present at any moment of disease duration which had an independent effect on mortality were the severity index, heart failure and steroid therapeutic index. The effect of infection, previous admissions, disease duration and late diagnosis was lost after this analysis. In other words, after controlling for other variables, the effect of the cumulated steroids index persisted. Independently of severity, activity, heart disease, etc., steroids were an independent factor related to death. This could be explained by the fact that higher steroids and maintained exposure are related to several comorbid conditions (i.e.,coronary artery disease, diabetes mellitus, psychosis/cognitive impairment) and also with a higher risk of infections, cardiovascular disease, fractures, pneumonia, thrombosis, etc.

Cutaneous involvement and chloroquine treatment were protective factors against death. This may be explained by several reasons: the use of chloroquine has some effect related to remission in SLE patients (29, 30). These drugs also have a benefit effect over atheroesclerosis, lipids, and coronary artery disease in lupus patients (31, 32). Finally these patients could represent a subset of "mild" lupus, with cutaneous and articular involvement, but no serious multi-organ damage.

Regarding disease duration, we found some differences between cases and controls; controls had a longer disease with a marginal difference ($p = 0.07$), but when this variable was included in the multiple logistic regression models, the statistical significance was lost. This difference may be due to the disease duration was matched by ±5 years. With these considerations, the results of our analysis showed that both cases and controls were comparable, because there were no meaningful differences between them. Another possible cause of bias is that cases and controls were taken from in-patients, so we had patients and controls with high score in both the severity and activity indexes. In this way, our data represent a cohort of selected patients with lupus who were seen in a tertiary care center from a developing country.

Some other variables, such as compliance, the ability to pay for medical care, or the results of immunological tests carried out at the moment of death, were not analyzed because of the design of our study. We consider our results to be relevant because the autopsy study provided data regarding the cause of death in our SLE patients. However, we must add that some patients had more than one SLE complication that could have led to the death of the individual. Thus, we specifically determined a primary cause of death despite other associated pathological processes detected at autopsy.

We identified a secular tendency of the death causes, in a similar fashion to other reports (9-12). Among patients with SLE who died between 1960 and 1970 the most common cause was uremia secondary to renal failure. In contrast, patients with SLE in the most recent two decades died of cardiovascular disease and infections. The mean disease duration in our cases was 4.0 years, but with a wide range of 2 weeks to 45 years. Thus an informed bimodal mortality pattern (5) was detected in our series, with infections and activity as the causes of early mortality and myocardial infarction as the cause of late mortality. A note of caution is necessary, however, when interpreting retrospective disease activity evaluations. We have shown that these values tend to show lower scores than prospective evaluations (34), but higher levels of disease are not missed. A relevant result was the presence of infection as a cause of early and late mortality; these findings are similar to those from Toronto (33), Afro-Caribbean (7), Chilean (8) and Singapore (9) patients with SLE. On the other hand, these data reflect the great heterogeneity of SLE patients attending our hospital.

Acknowledgements

The authors would like to thank Ms. Blanca Ariza Hernández for her invaluable help in finishing this paper.

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