THE EFFECTS OF ETHNICITY, SOCIOECONOMIC STATUS AND AUTOANTIBODIES ON CLINICAL OUTCOME IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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The Effects of Ethnicity, Socioeconomic Status and Autoantibodies on Clinical Outcome in Patients with Systemic Lupus Erythematosus

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CHAPTER 1

Systemic lupus erythematosus (SLE) is a clinically heterogeneous autoimmune disease with multi-organ involvement. Disease severity is variable ranging from relatively mild disease to organ and life-threatening disease. The incidence of SLE is increasing and current estimates of disease prevalence range from 12-50/100,000 of the general Caucasian North American population (1;2). The incidence and prevalence are highest in women between the ages of 15-45 when the ratio of women to men involved is approximately 12:1. In contrast, in pediatric and older-onset lupus, the female to male ratio is closer to 2:1. The prevalence of SLE also varies globally and among different ethnic backgrounds. African Americans, Asian Orientals and certain Native North American (First Nations) populations have a higher prevalence of SLE than populations that are primarily of Caucasian background suggesting ethnicity, either genetics or cultural issues, may play a role in disease pathogenesis.

The mortality of lupus has improved from a 5 year survival of 50% in 1955 to a 10 year survival of 90% in the 1990s(3;4), likely related to improvements in detection and the use of immunosuppressive therapy; however, mortality is still 3-5 times higher than in the general population. Early mortality is often due to active disease in particular renal or neurological involvement, while late mortality is usually due to complications from disease related organ damage or due to the adverse effects of treatment. Disease activity is predictive of later organ damage at 3 and 5 years (5) and early evidence of organ damage is a strong predictor of future organ damage (6) and premature death (7). Thus it is evident

that early intervention is needed to control disease activity and hopefully prevent organ damage.

Markers are needed in order to distinguish patients destined to have more severe disease requiring aggressive immunosuppression from those with milder disease and to identify potentially correctable disease modifiers that may be important in reducing the morbidity and mortality in this relatively young population. Markers of disease severity are likely to be biologically relevant to the disease pathogenesis whereas disease outcome may also be affected by non-biological factors.

SLE is an autoimmune disease characterized by the excessive and abnormal production of autoantibodies, immune complex deposition and immune mediated tissue injury (8). Biomarkers reflective of these processes may be of benefit in determining disease susceptibility or the potential for organ involvement. Autoantibodies are the hallmark of SLE and specific autoantibodies that can be measured in a clinical setting may be of use in predicting SLE outcome. Of particular interest are antibodies directed towards double stranded DNA (dsDNA) and to extractable nuclear antigens (ENA). Additional novel biomarkers that may be useful in identifying disease susceptibility or specific organ involvement are currently being investigated and the current status of some of these potential biomarkers has been recently reviewed (9;10). The clinical utility of the majority of the biomarkers identified in these reviews has not yet been confirmed and the majority are available only through research protocols.

Non-biological factors are important determinants of health and known to impact on the outcome of many chronic conditions. Specifically, socioeconomic status (SES), which is affected by multiple factors including education level, income, and type of occupation can affect health related behaviors, attitudes to health care, and potentially affect access to or compliance with health care interventions. Poor SES has adverse effects on chronic conditions such as diabetes and there is evidence to suggest it may also adversely affect SLE outcome.

Thus, several factors are potentially important in determining disease severity and outcome as reflected by measures of disease activity, end organ damage and mortality. This thesis will review the published literature addressing the roles of ethnicity, socioeconomic status and autoantibody profile, in particular antibodies to extractable nuclear antigen, in determining morbidity and mortality in SLE. In addition, a systematic review of the literature studying ENA associations with clinical features will be presented as well as a formal analysis of the roles of ethnicity, socioeconomic status and antibodies to extractable nuclear antigens on clinical outcomes in the Manitoba Lupus population.

CHAPTER 2

The role of genetics in SLE

Ethnic differences in the prevalence and severity of SLE have been reported. African Americans, Hispanics, Afro-Caribbeans, Asian Orientals and Native North American Indians (First Nations) have all been shown to have a higher incidence and severity of SLE compared to Caucasians of the same areas. In contrast, SLE is rare in West and Central Africa. (11;12) (13;14). This variability may relate to differences in genetic background or environmental and cultural influences. In the case of lupus in patients of African ancestry, the increasing prevalence gradient of lupus in populations from Africa to Europe or North America suggests that a potential interaction between genetic background(s) or the admixture of genetic backgrounds and environmental influences may contribute to the development of SLE (15;16).

Similarly, Hispanic populations from the USA, Latin America, and Mexico have also shown differences in SLE severity, autoantibody production and genetic background(17-22). Many of these findings have been demonstrated through a multicenter collaborative study: the Lupus in Minority Populations Nature versus Nuture (LUMINA) and many of the LUMINA findings have been supported by a recent large multicenter cohort from Latin America: the Grupo Latinoamericano de Estudio del Lupus (GLADEL) study (23). Comparisons of Hispanics from continental USA (Texas) and the island of Puerto Rico analyzed by the LUMINA study have shown higher disease activity, more organ involvement, higher frequency of anti-dsDNA autoantibodies, and more damage accrual in patients from Texas(21). Although these differences were mediated by several factors

including genetics, environmental factors and social factors, genetics appeared to be the most important. Hispanics have mixtures of Western European (mainly Spanish), African and Amerindian ancestry although the influences of each ancestry vary between Hispanic subpopulations. Hispanics from Texas are believed to have a higher proportion of Amerindian ancestry, primarily Aztecs and Mayas, while Hispanics from Puerto Rico may have Tainos background. The authors of this work suggest that the greater severity of lupus in Texan Hispanics may be related in part, to Amerindian genes.

Native Americans (First Nations) share genetic ancestry with Asian-Orientals. Similar to Asian Orientals, several Native American groups have been shown to have an increased incidence and prevalence of lupus compared to Caucasians. Disease severity varies in groups with high disease prevalence with some Native American (First Nations) groups having relatively mild disease and others quite severe disease with high frequencies of serious end organ involvement (reviewed in (13)).

Specific genetic associations in lupus have been studied by determining the associations of individual gene alleles with disease and by genetic linkage studies that associate chromosomal regions with disease. Like other autoimmune conditions, multiple genes are likely required to develop SLE. Potential candidate genes would likely contribute to disease susceptibility and the induction of autoimmunity, immune specificity, or the individual host response. Several lupus- associated genes have been identified that relate to histocompatibility HLA haplotypes, complement components and cytokines, and immunoglobulin receptors. In addition, specific features of SLE may have genetic

predispositions. Interpretation of genetic associations in lupus is difficult in many cases due to concerns of linkage disequilibrium in which there is close association of the marker gene with a different possibly unidentified gene. However, true associations between HLA class II products DR3 and DR2 and possibly DQA with lupus have been found. In addition, there appear to be independent associations with complement genes, which are also located in the DR locus, and lupus. More recently, associations of the immunoglobulin Fc receptor haplotypes with lupus and lupus nephritis have been identified. The immunoglobulin Fc region influences the affinity of immunoglobulin binding to receptors and thus Fc polymorphisms have the potential to enhance or suppress antigen specific immune responses which are important in the pathogenesis of lupus. Genetic linkage studies have also identified regions on chromosomes 1, 2, 4, 6, and 16 which appear to have relatively strong associations with lupus indicating that additional susceptibility genes are present that are not yet identified (24).

CHAPTER 3

The role of socioeconomic status in lupus

Socioeconomic status (SES) is an important influence on health status especially for chronic medical conditions. It can affect access to and compliance with health care interventions, attitudes to health care and health related behaviors. Determining the specific role of SES on rheumatic disease outcomes is often challenging because in many populations it tends to be associated with specific ethnic groups with potential genetic confounders (reviewed in (25;26)). Several groups have investigated the role of SES on lupus related mortality, organ damage and disease activity (Table 3.1). The results of these studies have been contradictory, possibly due to methodologic differences in the measures used to ascertain SES, the ethnic populations studied and the difficulty separating ethnicity from SES. Many of the populations that have more severe forms of lupus including the Hispanics, African Americans and First Nations populations often have lower SES measures. The influences of economic and social support have been studied primarily in the United States where lower economic status can be a significant barrier to health care access and compliance. In Canada and Britain, health care is publically funded, including a proportion of prescription costs, thus access to care due to economic reasons is less restricted. This system allows a more controlled analysis of the role of SES on SLE outcome without access to care limitations. In one retrospective Canadian study of 78 Lupus patients, SES did not influence Lupus outcome (27). Similarly, in a European population, ethnicity but not SES affected prevalence and incidence of SLE (28). Despite the discrepancies seen in studies of SES effects on SLE activity or outcome, the majority of evidence suggests that SES does play a significant role in determining the morbidity and

mortality related to SLE although this may be more important in health care systems where SES affects access to medical care.

Mortality

Seven studies (4 separate multicenter cohorts and 1 census study) were identified that examined the role of SES on mortality related to SLE. A large retrospective multicenter study from the United States found that survival varied with SES (source of health care payment) as well as with clinical features but not with race after correction for SES (29). In this study, disease related clinical features were more important than SES in stepwise analysis. The survival of an inception cohort of patients with early disease (<2 years since diagnosis) followed for 15 years was studied and reported after a mean disease duration of approximately five years and subsequently after 15 years (30-32). Initial analysis indicated SES (medical insurance) and ethnicity (primarily Caucasian vs African American but including 2 NAI and 1 Polynesian) contributed to early mortality. The subsequent report which provided longer followup and more detailed SES analysis (medical insurance and income) found the primary predictor of mortality was SES and increased age, but not ethnicity. Neither study controlled for disease related activity nor organ damage. Cohorts from the University of Alabama at Birmingham and University of Texas Health Science Center that have formed the core cohorts of the LUMINA studies have shown initially that ethnicity and clinical features but not SES (medical insurance) influenced mortality (33). More detailed analysis of SES (poverty, education, occupation) in a subset of these patients with less than 5 years of disease found that poverty was an independent contributor to early mortality in addition to disease related activity and organ damage (34). A large multicenter cohort study from Latin America found education, SES, and medical insurance were

predictive of death on multivariate analysis in addition to damage scores and country (23). Using US census data, Walsh and DeChello found an increased SLE related mortality rate in counties with lower SES and higher Hispanic populations although the influence of ethnicity was not separated from SES(35).

Organ damage

Nine studies (4 multicenter cohorts, including one from the UK and Canada), examined organ damage as measured by the Systemic lupus International collaborating clinics/American College of Rheumatology damage index (SLICC/ACR)(36;37), a widely used global measure of organ damage, or its components. Lower occupational prestige at diagnosis was independently associated with greater damage on multivariate analysis after correcting for race and disease activity (38) however, in a followup study of this cohort, SES was not associated with SLICC components (39). In the LUMINA cohort, poverty in African Americans was associated with higher SLICC damage scores(19). Education, poverty and marital status were independently associated with lupus nephritis in this cohort, however on multivariate analysis, only marital status remained significant (40). Calvo-Alen et al in a study of two Hispanic groups, one likely part of the LUMINA cohort and another from Spain, found that greater home density but not other SES variables differed between the two populations and was associated with damage after 4 years(22). Similar associations with poor SES and greater damage were seen when SES was measured using the Hollingshead Two-Factor Index of social position which combines occupation and education (41), when education level was compared to musculoskeletal damage (42)

and in a cohort of Canadian and UK SLE patients whose health care is publically funded (43).

Disease activity

The Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)(44), the Systemic Lupus Activity Measure (SLAM)(45) and in Europe, the British Isles Lupus Assessment Group (BILAG)(46) are the instruments most commonly used to assess disease activity. These indices measure global disease activity as well as activity of individual organ systems. Lower SES measured by education, income, insurance and access to care was associated with greater disease activity in the LUMINA cohort, other US cohorts and in Hispanics with less medical coverage but not in cohorts from Canada or the UK. Lupus nephritis, the most common clinical feature identified was not more frequent in patients with lower SES in the majority of studies. Only studies of Hispanics in the US (the LUMINA cohort) found associations with low SES and nephritis.

The influence of SES on lupus outcome while difficult to separate from ethnicity appears to be an important determinant of lupus outcome especially in health care environments where low SES is potentially a significant barrier to accessing health care. The most appropriate measure of SES is not clear and different facets of SES, namely education, income, or locale, likely influence clinical outcome in different ways. For instance, education may influence a patient's initiative to investigate their symptoms or disease whereas income or poverty may influence ability to access or comply with care. This highlights the need to address social or non-biological factors in addition to biological

factors when assessing lupus patients and has potential implications for designing patient education programs and developing health care funding policies.

Table 3.1 Studies of socioeconomic status and lupus clinical outcome

Study	Population	Outcome	Variables	Result
Ginzler (29) 1982	SLE 1103 multicenter	Mortality	SES Health care coverage Geographics Ethnicity	Survival influenced by SES (health care coverage) proteinuria and Hct) No association for race when corrected for SES
Studenski (30) 1987	SLE (early) 411 within 2 years of onset) Caucasian 211 African American 197 Other 3	Mortality	SES Medical insurance Ethnicity	Mortality affected by race and SES
Ward(47) 1995	Inception cohort Caucasian 211, African American 197	Mortality	SES Medical insurance Income Demographics Ethnicity	SES, advanced age associated with mortality No effect of ethnicity, gender
Reveille(33) 1990	SLE 389 Caucasian 184 African American 203 Asian 2	Mortality	SES Medical insurance Ethnicity Clinical features	Ethnicity (AA), age of onset and clinical features affected mortality No effect of SES
Alarcon (34) * 2001	Lumina Study SLE 288 34 deaths 11 infection 14 SLE	Mortality	SES Education, income, occupation, Health behaviors Immunogenetics Ethnicity Clinical features Disease activity (SLAM)	Mortality increased with poverty, disease activity and organ damage.
Walsh(35) 2001	SLE deaths combined with census data for all 3111 USA counties	Mortality	Census data Ethnicity Income	Mortality rates highest in USA counties with poorer SES and higher Hispanic populations

Pons-Estel(23) 2004	GLADEL inception cohort (1214) White 507 Mestizos 537 African-Latin American 152	Mortality Organ Damage (SLICC) Disease activity (SLEDAI)	SES Graffar scale (family occupation and education, primary source of income, housing, neighborhood) Education Type of medical care Ethnicity Clinical features	Mortality increased with low SES, less education, poor medical coverage Damage greater with lower SES Disease activity affected by SES (low education, less medical coverage)
Alarcon (19) * 2001	Lumina Study SLE 288 Hispanics 72 African American 104 Caucasian 82	Organ damage (SLICC)	SES Education, income, occupation, Health behaviors, Immunogenetics, Ethnicity Clinical features and disease activity (SLAM)	Organ damage increased with ethnicity, disease activity, poverty (in AA) and abnormal health behaviors
Calvo-Alen (48) * 2003	Hispanics USA 52 Spain 28	Organ damage (SLICC) Disease activity (SLAM)	SES Income, education home density, Clinical features Immunogenetics, Serology, Psychosocial behaviors	Hispanics with Amerindian background have more serious disease Increased home density (low SES) associated with damage and activity over time
Bastian(40) * 2002	SLE	Organ damage (SLICC-lupus nephritis)	SES Income, education home density, Clinical features Immunogenetics, Serology, Psychosocial behaviors	Nephritis more common in Hispanics. Serology, disease activity, socio-demographic features (including income and education) affected LN

Bae (49) 2001	SLE 200 cross-sectional multicenter	Organ damage (SLICC) Disease activity (SLAM) Health status (SF36)	SES Demographics Clinical features Psychosocial behavior	Higher social support associated with improved physical indices and better mental health Best intervention for social support in pts with better SES?
Rivest (39) 2000	SLE 200 cohort multicenter balanced for race and SES	Organ damage (SLICC)	SES Insurance, income education Disease activity (SLAM) Clinical features	Clinical variables correlated with SLICC No association with SES
Sutcliffe (43)@ 1999	2 centers 195 SLE patients	Organ damage (SLICC)	SES education income employment Disease activity (SLAM/SLEDAI) Social support (ISEL) Patient satisfaction (SPQIV)	Non-Caucasian race, lower education and higher disease activity associated with greater organ damage
Lotstein (41) 1998	SLE 100	Organ damage (SLICC) Disease activity (SLAM/ SLEDAI)	SES Hollingshead Index (occupation/education) Psychosocial Health status	SES associated with SLICC No association with SLAM/SLEDAI
Karlson(38) 1997	Retrospective cohort 200 pts	Organ damage (SLICC) Disease activity (SLAM)	SES Income, education, insurance Psychosocial/ behavior Clinical factors	Organ damage associated with age, disease duration, occupation Disease activity associated with psychosocial factors.
Petri (42) 1995	SLE 409 Hopkins Cohort	Damage musculoskeletal	SES	AA and low SES more likely to have MSK damage

Molokhia (50) 2003	SLE 124 Control 219	Outcome: diagnosis of SLE	SES Education Household amenities	Risk of SLE due to genetics, not environmental factors
Hopkinson(28) @ 1993	SLE Prevalence 200 Incidence 23	Prevalence/incidence of SLE	SES Occupation Index (income, education, residence, housing) Ethnicity	Higher prevalence in Afro-Caribbean Similar SES profile to general population
Reveille (17) * 1998	SLE 229 prospective multicenter (LUMINA)	Disease activity at onset (SLAM, MD global)	SES Income, education, insurance, access to care Immunogenetics Ethnicity Clinical features	Disease activity associated with SES, ethnicity and HLA type Ethnic differences in clinical features, HLA
Alarcon (20) * 1998	SLE 229 prospective multi center (LUMINA)	Disease activity (SLAM)	SES Income, education, insurance, access to care Immunogenetics Ethnicity Clinical features Psychosocial behaviors	Disease activity associated with SES, ethnicity, anti-Ro, HLA type (DRBI0301) and poorer psychosocial behaviors.
Karlson (51) 1995	Random sampling of multicenter cohort SLE 99 balanced for ethnic group and insurance	Disease activity (SLAM)	SES Insurance, occupation, education, income, employment	Lower SES associated with greater disease activity
Johnson (52)@ 1994	SLE 209 Brazil 33 England 112 Sweden 64	Disease activity (BILAG)	SES occupation Ethnicity	No SES effects. patients in Brazil had increased renal involvement
Esdaile (27) @ 1988	Prospective cohort Caucasian 67 African-American 8 Oriental 3	Disease activity (AIMS)	SES British Census Scale Education Laboratory features	SES did not affect disease activity

Alarcon (53) * 2004		Disease activity (SLAM)	SES "Wealth" poverty medical insurance education	SES (but not wealth) affected disease activity
Hopkinson (54)@ 2000	SLE 189 (Afro-caribean, asian, caucasian)	Clinical features proteinuria	SES Ethnicity Serology	Ethnicity affected proteinuria (Afro-Caribbean) not serology
Rzany (55) 1991	SLE 281 (Hopkins cohort)	Clinical features Renal insufficiency		SES, ethnicity or serology did not influence renal disease
Petri (56) 1991	SLE 198 AA 115	Clinical features		No association of SES or ethnicity with morbidity
McAlindon (57) 1993	SLE 296 cross sectional survey	Clinical features nephritis	SES Ethnicity "endocrine"	Lower social class, West Indian ethnicity influenced nephritis
Alarcon (18)* 1999	SLE Incident 56 Prevalent 173	Clinical features	SES Ethnicity Autoantibodies	Hispanics and AA were younger, had lower SES more renal CVD and active disease. Different Ab
Bastian (40)* 2002	SLE 353 pt multicenter Hispanic 65 AA 93 Caucasian 91	Clinical features nephritis	Social-demographic Clinical Immunological Immunogenetic Health habits	LN more common in Hispanics, AA. Single, RNP positive, clinical and immunogenetics predict lupus nephritis
Ward (58) 1992	Retrospective 160 SLE nephritis patients	Clinical features lupus nephritis	SES medical insurance education Age and gender Ethnicity Smoking HTN	No effect of demographic or SES
Barr(59) 2003	Retrospective cohort 128 biopsy-proven LN	Clinical features Lupus nephritis creatinine doubling	SES neighborhood, medical insurance, poverty Ethnicity	Poverty is risk factor for LN disease progression

Ward(32) 1990	Retrospective AA 160 Caucasian 174	Clinical features	SES Ethnicity Antibodies	AA more CNS, serositis, and renal lupus, SM and RNP positivity
Callahan (60) 1990	124 Consecutive 93 Caucasian	Clinical outcome by: ADL difficulty, dissatisfaction, pain Rheumatology attitudes index Global health assessment	SES education Ethnicity Gender	Less education associated with poorer clinical outcome

* LUMINA study
@ Canadian or European study (public health care)

CHAPTER 4

The role of autoantibodies in lupus

One of the pathognomonic features of lupus is the production of autoantibodies, the majority which are directed towards components of the cell nucleus. The presence of anti-nuclear antibodies (ANAs) is highly sensitive but not specific for SLE. ANAs can be demonstrated in over 95% of patients with SLE and are included in the criteria used to make a clinical diagnosis of SLE. Although ANA titers often fluctuate during the course of SLE, serial measurement of ANA is not very useful for following disease activity nor for stratifying or identifying patients at risk for more serious disease or particular end-organ involvement.

Autoantibodies that are more specific for SLE, may be associated with specific manifestations of disease, and are available clinically include antibodies to double stranded DNA (dsDNA) and antibodies to extractable nuclear antigens. Antibodies to dsDNA are part of the diagnostic criteria for SLE and are more specific (95%) but less sensitive for SLE than ANAs. They can be detected in approximately 60% of SLE patients. Titers of dsDNA may fluctuate with disease activity and have been reported to be associated with lupus nephritis however many patients with dsDNA do not develop renal lupus.

Antibodies to extractable nuclear antigens (ENAs) are directed towards ribonuclear complexes found within eukaryotic cell nuclei. The ENAs currently measured in clinical practice are anti-Ro, anti-La, anti-Smith (anti-SM) and anti-ribonuclear protein (anti-

RNP). Lupus patients may develop antibodies to a single ENA or may have multiple ENA antibodies. Anti-Sm and anti-RNP are often seen in combination as are anti-Ro and anti-La. The existence of the two major categories, the anti-SM/ anti-RNP antibody class and the anti-Ro/ anti-La antibody class, is likely related to their respective antigen complexes.

SM-RNP antigen complex

The anti-SM and anti-RNP antibodies recognize different components of the U1 ribonuclear protein particle (snRNP) found in the cell nucleus (61). The U1snRNP complex is composed of a single uridine rich U1 RNA strand complexed with several proteins; U1-70kd (70kd), A (33kd), C (23kd), and the SM core complex or 6S particle which contains the B'/B (29,28 kd), D (16kd), E (12kd), F (11kd) and G (10kd) proteins (62;63). The U1-70 kd, A, C complex is specific to U1snRNP however the SM core complex is present in other U-RNA particles. Anti-RNP antibodies are directed towards the U1-70kd, A, C complex whereas anti-Sm antibodies recognize the SM core complex (64). The U1snRNP complex is involved in the processing of heterogeneous RNA into mature messenger RNA (mRNA)(65). It combines with other proteins to form the spliceosome, a complex that recognizes intron and exon junctions in RNA and then splices and recombines RNA sequences to form mRNA (66). Messenger RNA is then available for protein synthesis.

Ro/La antigen complex

The antigens recognized by anti-Ro and anti-La form a complex composed of a small RNA molecule (hY1, hY3, hY4, or hY5), the Ro 60kd protein, and the La protein (48kD). An additional Ro 52kD protein has an unspecified interaction with the Ro/La complex (61). The Ro protein may function in the RNA discard pathway (67). The La protein is a transcription-termination factor for RNA polymerase III (68).

Clinical relevance of SM and RNP antibodies

The prevalence of anti-Sm autoantibodies in patients with lupus varies from 5% in some Caucasian populations(69;70), to 30% in East Indian (71), Arabian(72) and Asian (73) populations and up to 47% in certain African American(74) populations. Those SLE populations with a higher prevalence of anti-SM antibodies seem to have a greater degree of renal involvement (74;75) and anti-SM antibodies have been shown to be a predictor of premature death in one series (see Chapter 6) (76). However, the association of anti-SM and renal or other end organ involvement is still unclear. Although published studies have demonstrated relative risks (RR) of renal disease occurring in patients with anti-SM antibodies of up to 5.73 (77), others have not found such an association (78;79).

An association of anti-SM antibodies with neurologic lupus has also been proposed however again, there is discrepancy between the published studies with some finding associations (RR= 4)(80) and others not(78;81). The prevalence of anti-RNP antibodies in lupus populations varies from 10% in Caucasian(69) to 25% in African American populations and 60% in some series of East Indian lupus patients (82). As with anti-SM

antibodies, the true clinical significance of RNP autoantibodies is unclear. Several studies have reported a strong association of RNP antibodies with Raynauds phenomenon, however, reported clinical associations of RNP antibodies with neurologic involvement, arthritis, serositis, and photosensitivity have not been consistently seen in different cohorts. Interestingly, some studies have suggested that the presence of anti-RNP may be protective for renal lupus(79;83).

Clinical relevance of Ro and La antibodies

Anti-Ro is the commonest ENA occurring in 60-90% of SLE patients in some series (61). Anti-La is often associated with anti Ro (84)but occurs in only 15-50% of SLE patients (61;85). Anti-Ro antibodies are associated with an increased risk of skin involvement especially photosensitivity (RR 1.63 1.38-1.93) and secondary sjogren's syndrome. Neonatal lupus, which includes congenital heart block and a transient lupus skin rash, has a strong association with maternal anti-Ro antibodies. This appears to be increased with higher titers of anti-Ro or if anti-52kD Ro or anti-La are also present(86).

Prediction of disease activity

Surrogate markers of disease activity are useful to clinicians by providing a means to predict flares of disease that may require more aggressive therapy. Anti-SM antibody titers appear to fluctuate over time and may serve as such a surrogate marker. However, although the titers of anti-SM antibodies appear to correlate with disease activity in some small series(73), others have found little variation in titer level when patients are followed over time and no correlation with titer and clinical activity (87;88). Similar small studies of

anti-RNP titers have also failed to consistently show a correlation with various non-standardized markers of disease activity (88;89). In one series of only 10 patients followed for 1-10 years, anti-Ro levels appeared to increase with disease activity in some but not all patients (90). Studies to date have been largely done with small numbers of patients thus a larger population based longitudinal study is needed.

HLA associations with ENAs

Susceptibility to SLE and ENA production is strongly influenced by HLA subtypes. Ro and La autoantibody production is associated with the DR3 and DR2 haplotypes. Anti-Ro without anti-La production is increased in individuals who have the HLA haplotype DR2/DQw1 whereas anti-Ro with anti-La is increased in the DR3/DQw2 haplotype. This effect appears to be dose dependent with heterozygotes expressing DR2/DQw1 and DR3/DQw2 having high titers of anti-Ro antibodies. (91;92). HLA associations have also been found for RNP and SM autoantibody production (93). RNP and SM autoantibody production appears to be influenced by DR4 and DR2. The frequencies of HLA-DR4 and HLA-DRw53 were greater in anti-RNP positive patients compared to RNP negative patients (94). In addition, African American patients positive for DQw6 associated DQA1.0102 or DQB1.0602 were likely to be SM positive (OR of 6.7 and 9.1 respectively) whereas DQw5 associated DQA1.0101 and DQB1.0501 were associated with RNP positivity (OR 5.5 and 23.3 respectively). Caucasian lupus patients with DQw8 associated DQB1.0302 or DQw5 associated DQA1.0101 and DQB1.0501 were more likely to be RNP positive (OR 4.2) (95). Thus differences in HLA types may contribute to the ethnic variation in ENA expression and clinical features.

CHAPTER 5

Meta-analysis of clinical associations and ENAs

The clinical associations reported for specific antibodies to extractable nuclear antigens (ENAs) in particular anti Ro, anti-La, anti-SM and anti-RNP, suggest that measurement of these ENAs may be useful to predict patients destined to have certain clinical manifestations of their SLE, either at presentation or on future follow-up. Numerous studies have measured ENAs and correlated serology with clinical features, often with discrepant results as described above. To determine the robustness of the associations of individual or combinations of ENA with specific clinical features a meta-analysis of the published literature was performed. Formal meta-analysis combines data obtained from multiple studies, weights the data according to sample size or other study quality, and provides a statistical summary of the studies. While mainly used for randomized clinical trials, methods are being developed for assessing diagnostic tests (96-98). This meta-analysis was conducted using these guidelines.

Methods

Study identification

Studies were identified by searching the electronic Pubmed/Medline database using both key MESH and non-mesh terms. (Appendix A) These terms included lupus, autoantibodies, specific antibodies and individual clinical features. The Cochrane Collaboration database was also searched; however, no studies were identified, probably because this database is primarily for clinical trials. Titles of research articles were reviewed to determine which abstracts were suitable for review. All selected abstracts were assessed to determine whether inclusion criteria were met. If at least partial inclusion

criteria were met, or there was insufficient information in the abstract to determine inclusion criteria, the paper was reviewed in detail. The majority of studies were published in English language journals. Those published in non-English journals were obtained where available and translated. All studies published before 2001 were considered for the analysis.

Included studies had at least ten adult subjects (18 years of age or older) with SLE as defined by ACR criteria (99;100)and presented sufficient data to calculate true positive rates (TPR) and false positive rates (FPR) for each antibody-clinical association. Only studies in which clinical features were defined by ACR criteria or validated outcome measurements for lupus such as the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Disease Damage Index (SLICC/ACR) and Systemic lupus erythematosus disease activity index (SLEDAI) indices were included. Clinical features were subsequently identified by system and by individual features (ie renal, proteinuria). For some comparisons, studies in which individual clinical features were not specifically defined by ACR criteria were also included in a separate analysis. No restrictions were applied to the method used to test for specific autoantibodies, however the method used was recorded for further sensitivity analysis.

Studies of patients with overlap syndromes, subacute cutaneous or discoid lupus (without systemic lupus) were excluded, as were studies using serum banks to identify SLE patients. Studies published only in abstract form were excluded.

Data extraction

Data was extracted from all studies meeting the inclusion criteria. Specific information obtained included the number of subjects in the study, the definition of each clinical outcome studied (which served as the reference standard), the number of subjects positive and negative for a specific antibody with the clinical feature and the number of subjects positive or negative for the antibody without the clinical feature. The majority of studies recorded antibody positivity as a dichotomous variable. A few studies reported a titer. This was converted to a positive or negative value using the titer cutoffs provided in the individual study.

Study quality was assessed by several means. The type of study, prospective or retrospective study, cohort or case control study was recorded. To determine study validity, the studies were reviewed to determine whether ENAs were measured independently of clinical assessments, whether ENAs were measured in all or a sample of the test population and how this population was chosen, and the method(s) used to measure the ENAs. These variables were used in sensitivity analysis. Additional information regarding the study population was also recorded including the clinic setting (tertiary care/University practice or community clinic), gender mix, disease duration and subject age. This information was collected in part, to determine the generalizability of the results.

Data Analysis

The meta-analysis was conducted using published guidelines for meta-analysis of diagnostic tests with the exception that a single reviewer extracted and analyzed the data (96-98;101;102). The specific autoantibody was treated as the diagnostic test and the

clinical feature as defined by ACR criteria, was considered the reference standard. The data was analyzed by two separate methods.

Data was initially analyzed using RevMan® 4.1 software. A fixed effects model was used as an extensive search was conducted to identify studies. Associations between clinical variables and individual or combination ENAs were determined by calculating relative risks (RR) and 95% confidence intervals (CI). Relative risks were chosen because the majority of studies were cohort studies. Associations were determined by comparing the number of individuals with the autoantibody having the clinical feature, to the number of individuals without the autoantibody having the clinical feature. Heterogeneity of associations was determined by Chi-squared testing using a p value of 0.1 (103). Sensitivity analysis of study quality was performed for comparisons where significant heterogeneity existed between studies. Data are reported as RR (95% CI).

Secondly, data was analyzed by creating summary receiver operating curves (sROC) and calculating a summary measure of diagnostic test accuracy, the Q*. The Q* statistic ranges from 0.5 (low accuracy) to 1.0 (high accuracy) and was calculated using the methods of Moses and Irwig (96-98;102). This method allows for variations in test threshold between studies. The false positive rate (FPR) and true positive rate (TPR) of each study were initially plotted to form the sROC. To determine the significance of the sROC curves, the Q* statistic was calculated for all studies, for studies with a true positive Rate (TPR) >0.49, and using the rigorous criteria of having a TPR >0.49 plus a false positive rate (FPR) < 0.50. The Q* statistic was determined by calculating the log odds of the false positive rate (FPR) and true positive rate (TPR) after increasing each observed frequency of true

positive, false positive, true negative and false negative by 0.5. An implied function of test threshold was calculated, U and V, these variables were plotted and a regression line was fitted to the points. The regression equation was used to calculate the Q* statistic. Calculations for the Q* calculation are shown in Appendix B. Data are reported as Q*. The sROC curves and Q* statistic were calculated for ENAs showing significant associations with renal or neurological lupus and for strongly positive associations found by RevMan® 4.1.

Results

The electronic search identified over 1325 potential articles and after reviewing titles, abstracts and published articles, 54 met the inclusion criteria. A repeat literature search performed in 9/03 identified four additional studies that looked at anti-SM clinical associations; however, only 1 met entrance criteria (Bastian 2002).

The majority of studies were cohort studies followed in University clinic settings. The mean study population (average of reported study averages) was 87 (range 10-331). The number of acceptable studies comparing ENA with specific clinical features varied from a minimum of 1 study to 21 studies. Comparisons were made only if at least three studies were available. The numbers of studies and sample size identified for each comparison are shown in Table 5.1.

Clinical associations with anti-SM

The association between renal lupus and anti-SM antibodies was investigated by thirteen studies, including 1494 subjects (78;81;104-114). A significant association between anti-SM antibodies and renal lupus was found (Relative Risk (RR) of a patient with SM having

nephritis of 1.28 (1.12-1.46) (overall effect z=3.57 p=0.0004) (Table 5.2, Figure 5.1). There was significant heterogeneity between the studies (chi squared 31 p<0.002). Although the majority of studies (ten) found a positive or trend to positive association, one study found a negative association (Boey) and two trended to negative associations (Al-Attia 1998, ter Borg). This difference did not appear to be due to the method used to detect anti-SM (Boey, immunodiffusion; Al-Attia, hemagglutinin; ter Borg, counterimmunoelectrophoresis), nor to the ethnic background of the subjects studied (Boey Asian Oriental; Al-Attia Arab; ter Borg Scandinavian). Overall, in this cumulative analysis, 22% of SLE patients were positive for anti-SM, 27% of nephritis patients had anti-SM whereas 18% of patients without nephritis had anti-SM (sensitivity 26%, specificity 82%, positive likelihood ratio: 1.5, negative likelihood ratio: 0.89).

The summary ROC curve for anti-SM and renal disease is shown in Figure 5.2. The Q* statistic calculated when all studies were included was 0.57 (low accuracy), and when only studies with TPR>0.49 and FPR<0.49 included the Q* statistic was 0.62 (moderate accuracy) (Table 5.3).

The association between neurologic lupus and anti-SM antibodies was looked at by 7 studies including 527 subjects (Table 5.2, Figure 5.3)(80;81;105;107;115-117). The presence of SM antibodies was significantly associated with neurologic lupus (RR 1.95 (1.44-2.63) overall effect z=4.37 p=0.00001). The majority of studies were small and there was significant heterogeneity between studies (Chi squared 19 p<0.005). This heterogeneity appeared to result from a single trial (Al-Attia 1996) that was weighted

heavily (23.5%) likely because of a high proportion of cases in a relatively small sample size. This study was the only one to show a trend to negative association between SM and neurologic lupus and used the hemagglutination method of detecting SM. In this study, the majority of neurologic lupus cases (21%) were headaches that are often difficult to attribute solely to lupus. Only 12 patients had psychosis, seizures, peripheral neuropathy, organic brain syndrome, myelopathy, stroke, or movement disorders. The cumulative analysis of all studies showed anti-SM had a low sensitivity (31%) and relatively high specificity (88%) for neurologic lupus with positive likelihood ratio 2.59 and negative likelihood ratio 0.78. The sROC curve for SM and neurologic lupus is shown in Figure 5.4. The Q* statistic including all studies was 0.60 (moderate accuracy). There were insufficient trials meeting stringent criteria for TPR and FPR (Table 5.3).

There was also a positive association between anti-SM positivity and the presence of arthritis (defined as arthritis, erosive arthritis or deforming arthritis, but excluding myopathy or arthralgias) (RR 1.47 (1.01-2.12) overall effect z=2.02 p=0.04) (105;113;118;119;119). The heterogeneity in this comparison was primarily from a single study (Franceschini) that looked at deforming arthropathy (Figure 5.5, 5.6).

No other significant associations were seen between anti-SM and clinical features.

Clinical associations with anti-RNP

The most significant clinical association with RNP autoantibodies was with Raynaud's phenomenon (RR 2.25(1.9-2.68) overall effect z=9 p<0.00001) (Table 5.2, Figure 5.7)

(81); (120). (121) (113;122-130)Significant heterogeneity was present primarily due to two studies that showed a trend to a negative association (Asero, Bresnihan). Both of these studies used immunoprecipitation (IP) to detect RNP autoantibodies. Despite this negative association in studies that were weighted highly in the meta-analysis, overall a significant positive association was still seen. The association of RNP and Raynaud's had a low sensitivity (41.9%) and moderate specificity (82.7%) with a positive likelihood ratio of 0.73 and a negative likelihood ratio of 0.29. When all studies were considered, the sROC curve was highly significant (Q* 0.98) (Figure 5.8, Table 5.3).

Musculoskeletal involvement including myopathies, arthralgias and arthritis was associated with RNP positivity (RR 1.09 (1.01-1.17)) however if only arthritis was considered this was no longer significant (RR 1.07 (0.97-1.17) (Table 5.2, Figure 5.9, Figure 5.10). The Q*statistic was 0.46 (poor accuracy) for RNP and arthritis when all studies were included and there were insufficient studies with TPR>0.49. Q* statistic for RNP and musculoskeletal associations (including myopathies and arthralgias) was modestly significant for studies with TPR> 0.49 (0.79) and studies with TPR>0.49 plus FPR< 0.49 (0.82) (Table 5.3).

No significant associations were seen between RNP and renal (Figure 5.11) or neurological lupus (Figure 5.12).

Clinical associations with anti-Ro

Significant associations were seen for Ro and photosensitivity (RR 1.35 (1.14-1.59) overall effect z=3.45 p= 0.0006) (131) (Figure 5.13, Figure 5.14)(132-139). The majority of

studies showed a positive effect or trend to positive effect with the exception of 3 studies (Dillon, Sutej, Smilke). The association of photosensitivity and anti-Ro had a sensitivity of 35.5% and specificity of 74% (positive likelihood ratio 1.37; negative likelihood ratio 0.87).

Most studies examined were cohort studies and thus RR were used to assess the associations between ENAs and clinical features. However, as a few included studies were case-control studies, associations were also determined using Odds Ratios (Table 5.2b). The same associations were found to be clinically significant with the exception of SM and arthritis which was no longer significant.

ROC curves were created for associations that were found to be significant by the RevMan analysis and for comparisons with the main clinical features for which significant associations were found (renal, neurological involvement, photosensitivity and Raynaud's phenomenon) and Q* statistic calculated. These are summarized in Table 5.3. Using the methods of Moses and the rigorous criteria of TPR>0.49 and FPR <0.5, significant ENA and clinical associations were seen for RNP and MSK (including arthralgias and myopathies) (Q* =0.82), RNP and Raynaud's phenomenon (Q*= 0.76), Ro and MSK (Q*= 0.85), and SM and renal (Q*= 0.62).

There were no significant clinical associations found for anti-La by RevMan analysis. The Q* statistic for anti-La and photosensitivity when all studies were analyzed was modest (0.62) (Table 5.3).

Discussion

Autoantibodies are a key feature of lupus and specific autoantibodies are associated with important disease manifestations in SLE. In particular, the presence of anti-SM antibodies is highly associated with renal and possibly neurologic involvement while the presence of anti-RNP antibodies is associated with Raynaud's phenomenon even in patients without overlap syndromes. Previously known associations of anti-Ro with photosensitivity were also confirmed. The current findings suggest that measuring autoantibodies may be of value in identifying patients at risk of developing significant end organ involvement but that they are not accurate enough to be used as diagnostic tests or to stratify treatment.

The studies identified in this analysis used a variety of methods to determine antibody positivity. These methods have evolved as biological knowledge and technical experience improved. Earlier studies often relied on gel precipitation (Ochterlony immunodiffusion or counter-immunoelectrophoresis). These techniques generally have good specificity but low sensitivity. More recent studies often used ELISA or immunoprecipitation techniques that generally are also specific but much more sensitive (140). Ideally, the same method would have been used in all studies and due to the differences in test sensitivities for detecting individual antibodies antibody- clinical associations may have been underreported.

Publication bias is always a concern when reviewing published literature as studies failing to find clinical associations are less likely to be published in accessible journals. In this study, although an extensive search of Pubmed/Medline database was performed other

databases such as EMBASE and published meeting abstracts were not searched. Thus it is possible that small studies may have been missed.

The methods for performing meta-analysis of diagnostic tests are still evolving and although general guidelines exist, the most appropriate method has not yet been clearly defined or validated. This meta-analysis assessed associations of autoantibodies with clinical features in two different ways with somewhat different results. The methods and software developed by the Cochrane Collaboration were primarily designed for analysis of randomized clinical trials and were adapted to the current clinical question to provide the Relative Risk or Odds Ratio of a patient with the antibody having the clinical feature. The majority of studies identified were cohort studies and thus overall the RR is more appropriate than the OR. The ideal diagnostic test would have both high sensitivity and specificity. The best method to analysis diagnostic tests uses receiver- operating curves (ROC) that compare true positive and false negative rates. Moses and Shapiro have proposed a method to critically evaluate the statistical significance of ROC curves created from compiling data obtained for multiple studies that use different thresholds for defining positive outcomes as was the case with the studies identified here. Although only studies that used ACR criteria for defining outcomes were included the outcomes differed. For instance, proteinuria and biopsy proven glomerulonephritis were both considered renal lupus. In addition, the methods used to detect autoantibodies varied in sensitivity and specificity. Using the Q* statistical method, the majority of antibody-clinical associations were of low or only moderate accuracy. The discrepancies seen between the two methods highlight the need to distinguish between clinical associations and diagnostic accuracy.

There is a need to identify accurate biomarkers of disease features and activity systemic lupus to assist clinicians in identifying patients at risk for more serious organ involvement and to follow disease activity longitudinally. Issues related to identifying such biomarkers for lupus have been eloquently discussed in recent reviews (9;10). Potentially useful biomarkers will likely be biologically based and be relevant to the immunopathology occurring at onset or during the disease progression.

Recent studies have demonstrated that autoantibodies can be detected in the sera of patients prior to developing clinical symptoms of SLE (141), that the number of autoantibodies detected also increases closer to the time of symptom onset and that certain antibodies, in particular anti- dsDNA, anti- SM and anti-RNP, occur later in evolution than others (ANA, anti-Ro, or anti-La) . This suggests a pathogenic role of autoantibodies in the development of lupus and indeed other autoimmune diseases associated with autoantibody production. The phenomenon of "epitope spreading" has been proposed to explain the development of various autoimmune diseases in particular SLE. In the appropriate genetically predisposed host, a specific environmental trigger is recognized by the immune system. The initial immune response is directed towards a specific antigen however, with ongoing antigen presentation, immune activation, and T cell involvement the epitopes or antigen profile recognized by the immune autoantibodies becomes broader. This continues until "pathological autoimmunity" develops, followed by clinical symptoms.

This model suggests autoantibodies may play a pathogenic role in the clinical features of SLE. Antibodies potentially can cause tissue damage through several mechanisms. Direct antibody mediated damage occurs when antibodies directed to cell surface membranes damage cells by complement mediated cell lysis or phagocytosis. Antibody-antigen complexes can deposit in tissue causing injury and antibodies may be able to penetrate cells and thereby interfere with intracellular functioning. Anti-Ro antibodies are believed to play a pathogenic role in both skin disease as well as neonatal lupus. In the case of lupus skin disease and neonatal lupus, anti-Ro antibodies are felt to recognize epitopes that are translocated to the cell surface potentially during apoptosis and binding to the cell may then trigger cell lysis. However, a direct pathologic role has not yet been identified for most antibodies.

Despite the limitations identified in this study, antibodies to extractable nuclear antigens remain a potentially relevant biomarker for susceptibility to specific features of lupus. In particular the presence of anti-SM antibodies suggests the potential for renal disease and may be involved in the pathogenesis of lupus related renal pathology. The identification of anti-SM or anti-RNP autoantibodies while not diagnostic of end organ disease should prompt a screen for renal and neurologic involvement and counseling for Raynaud's management. Future validation using standardized measurement techniques is required.

Figures

Table 5.1 Number of studies and total subjects studied for each clinical-autoantibody comparison. Musculoskeletal (MSK) includes only arthritis (myositis, arthralgias excluded).

	Neurological	Renal	Photosensitivity	Raynaud's	MSK	Hematological
Ro	3 (127)	12(1177)	9(657)	2	4(447)	2
La	3 (155)	8(813)	5 (329)	1	2	2
SM	7(527)	13(1494)	3(425)	2	4(403)	2
RNP	4(281)	21(2164)	5(433)	13(991)	9(956)	6(448)

Table 5.2a Effects sizes (Relative risks with 95% CI) for associations of ENA with clinical features

	Neurologic	Renal	Photosensitivity	Raynaud's	MSK	Hematologic
Ro	1.01 (0.58-1.75)	0.90 (0.78-1.04)	*1.35 (1.14-1.59)*	NA	1.27 (0.92-1.75)	NA
La	1.01 (0.56-1.8)	0.8 (0.6-1.06)	1.34 (0.94-1.91)	NA	NA	NA
SM	*1.95 (1.44-2.63)*	*1.28 (1.12-1.46)*	0.92 (0.68-1.23	NA	*1.47 (1.01-2.12)*	NA
RNP	1.24 (0.97-1.17)	0.99 (0.88-1.11)	1.03 (0.74-1.42)	*2.25 (1.9-2.68)*	1.07 (0.97-1.17)	0.95 (0.82-1.11)

Table 5.2b Effect sizes (Odds ratios with 95% CI) for association of ENA with specific clinical features.

	Neurologic	Renal	Photosensitivity	Raynaud's	MSK	Hematologic
Ro	0.78 (0.49-1.24)	0.84 (0.66-1.07)	*1.88 (1.26-2.79)*	NA	1.49 (0.9-2.47)	NA
La	1.01 (0.45-2.27)	0.72 (0.48-1.07)	1.82 (0.81-4.09)	NA	NA	NA
SM	*2.54 (1.33-4.86)*	*1.92 (1.29-2.88)*	0.97 (0.59-1.60)	NA	2.11 (0.97-4.58)	NA
RNP	0.92 (0.65-1.31)	0.98 (0.8-1.2)	1.04 (0.66-1.65)	*4.57 (3.28-6.37)*	1.31 (0.82-2.10)	0.88 (0.58-1.33)

Table 5.3 Summary of significant sROC curves by determined by Q* statistic

All studies	**TPR >0.49**	**TPR>0.49 + FPR<0.49**
SM –renal 0.57	SM-renal 0.62	SM-renal 0.62
SM- neuro 0.6	RNP-raynauds 0.76	RNP- raynauds 0.76
RNP- Raynauds 0.98	RNP- renal 0.70	RNP-MSK 0.82
Ro- Photosensitivity 0.64	RNP-neuro 0.52	Ro-MSK 0.85
Ro-MSK 0.57	RNP-MSK 0.79	
Ro- sicca 0.69	Ro-MSK 0.69	
La- photosensitivity 0.62	Ro- photosensitivity 0.63	

Table 5.4 Summary of sensitivities, specificities, positive likelihood ratios and negative likelihood ratios for significant associations between ENA and clinical features.
+LR: positive likelihood ratio –LR: negative likelihood ratio

	Sensitivity	Specificity	+ LR	- LR
SM-renal	26%	82%	1.5	0.89
SM-neurologic	31%	88%	2.59	0.78
SM-arthritis	37%	92%	0.40	0.69
RNP-Raynauds	42%	83%	0.73	0.29
Ro-photosensitivity	36%	74%	1.37	0.87

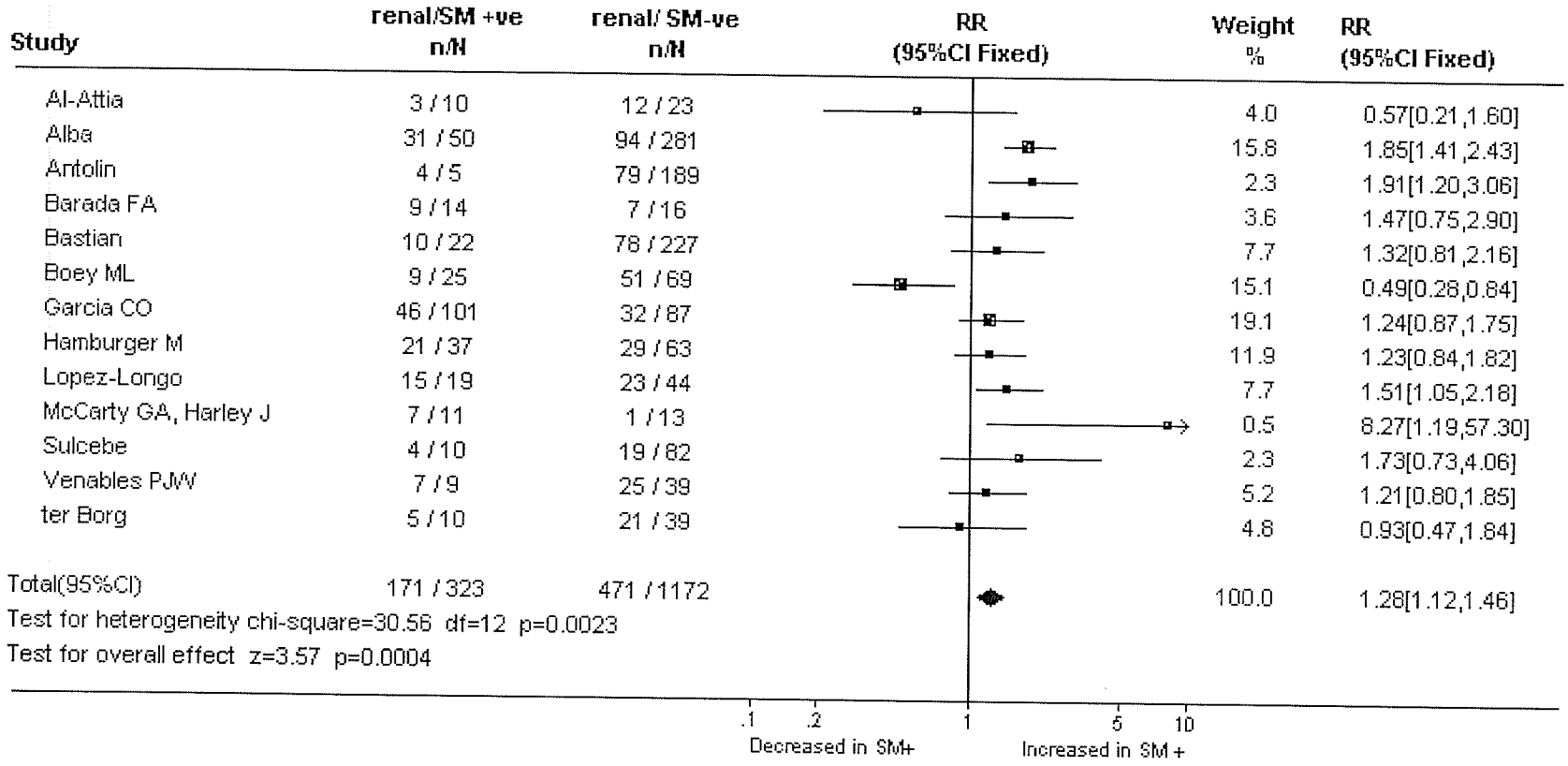
Study
renal/SM +ve n/N
renal/ SM-ve n/N
RR (95%CI Fixed)
Weight %
RR (95%CI Fixed)
Al-Attia 3 / 10 12 / 23 4.0 0.57[0.21,1.60]
Alba 31 / 50 94 / 281 15.8 1.85[1.41,2.43]
Antolin 4 / 5 79 / 189 2.3 1.91[1.20,3.06]
Barada FA 9 / 14 7 / 16 3.6 1.47[0.75,2.90]
Bastian 10 / 22 78 / 227 7.7 1.32[0.81,2.16]
Boey ML 9 / 25 51 / 69 15.1 0.49[0.28,0.84]
Garcia CO 46 / 101 32 / 87 19.1 1.24[0.87,1.75]
Hamburger M 21 / 37 29 / 63 11.9 1.23[0.84,1.82]
Lopez-Longo 15 / 19 23 / 44 7.7 1.51[1.05,2.18]
McCarty GA, Harley J 7 / 11 1 / 13 0.5 8.27[1.19,57.30]
Sulcebe 4 / 10 19 / 82 2.3 1.73[0.73,4.06]
Venables PJW 7 / 9 25 / 39 5.2 1.21[0.80,1.85]
ter Borg 5 / 10 21 / 39 4.8 0.93[0.47,1.84]
Total(95%CI) 171 / 323 471 / 1172 100.0 1.28[1.12,1.46]
Test for heterogeneity chi-square=30.56 df=12 p=0.0023
Test for overall effect z=3.57 p=0.0004
.1
.2
1
5
10
Decreased in SM+
Increased in SM+

Figure 5.1

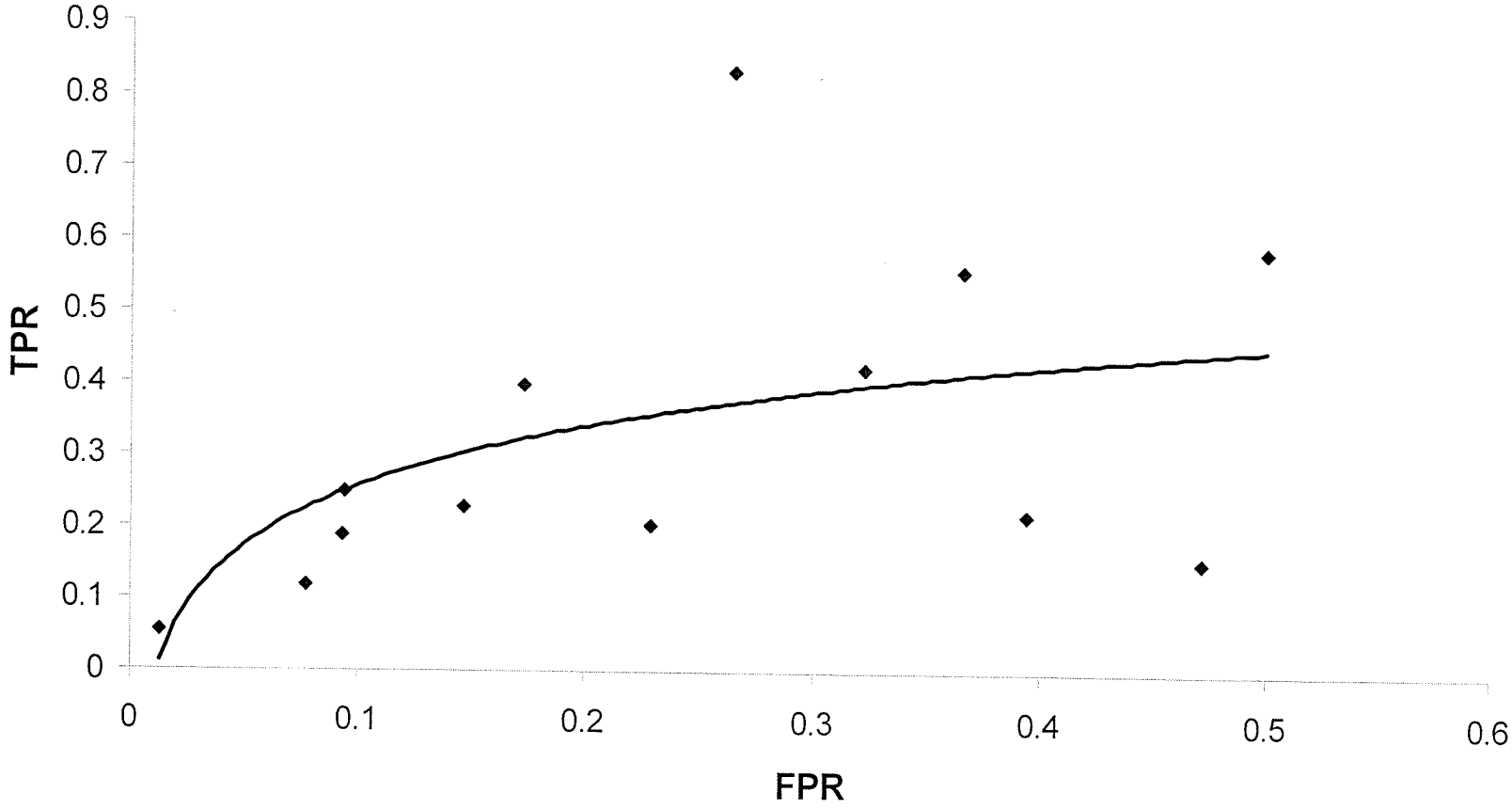

Figure 5.2

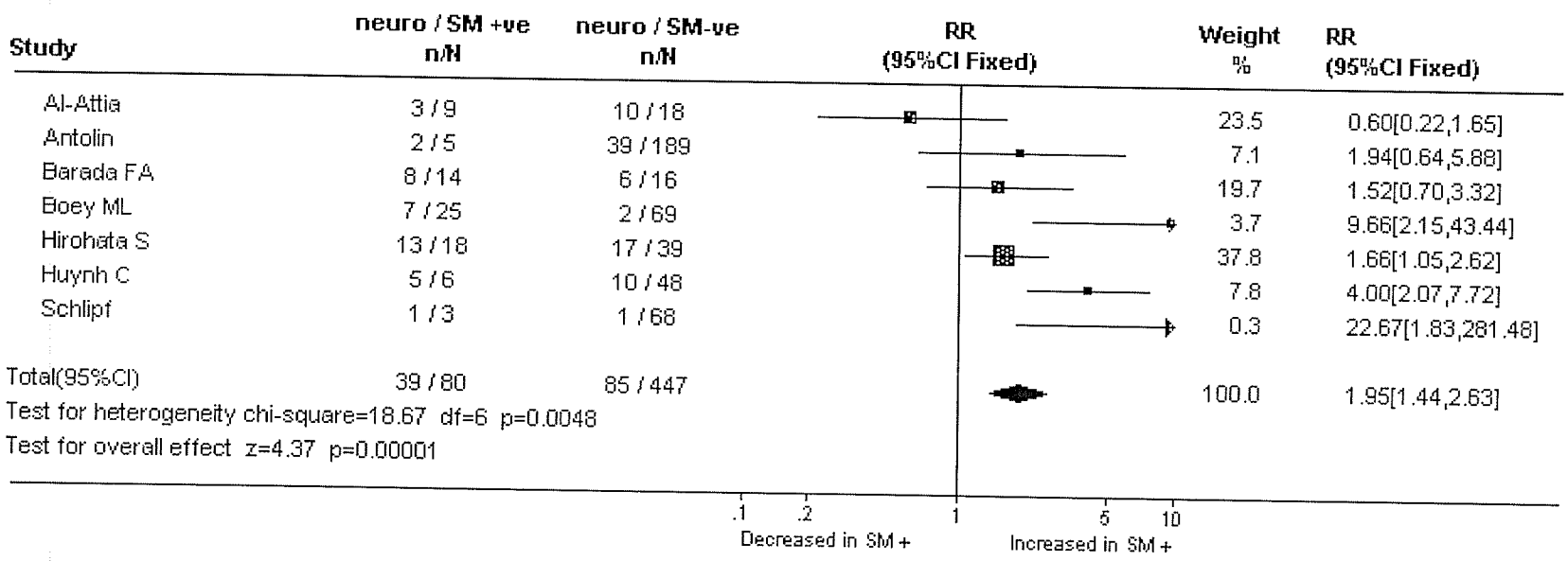
Study
neuro / SM +ve n/N
neuro / SM-ve n/N
RR (95%CI Fixed)
Weight %
RR (95%CI Fixed)
Al-Attia 3 / 9 10 / 18 23.5 0.60[0.22,1.65]
Antolin 2 / 5 39 / 189 7.1 1.94[0.64,5.88]
Barada FA 8 / 14 6 / 16 19.7 1.52[0.70,3.32]
Boey ML 7 / 25 2 / 69 3.7 9.66[2.15,43.44]
Hirohata S 13 / 18 17 / 39 37.8 1.66[1.05,2.62]
Huynh C 5 / 6 10 / 48 7.8 4.00[2.07,7.72]
Schlipf 1 / 3 1 / 68 0.3 22.67[1.83,281.48]
Total(95%CI) 39 / 80 85 / 447 100.0 1.95[1.44,2.63]
Test for heterogeneity chi-square=18.67 df=6 p=0.0048
Test for overall effect z=4.37 p=0.00001
.1
.2
1
5
10
Decreased in SM +
Increased in SM +

Figure 5.3

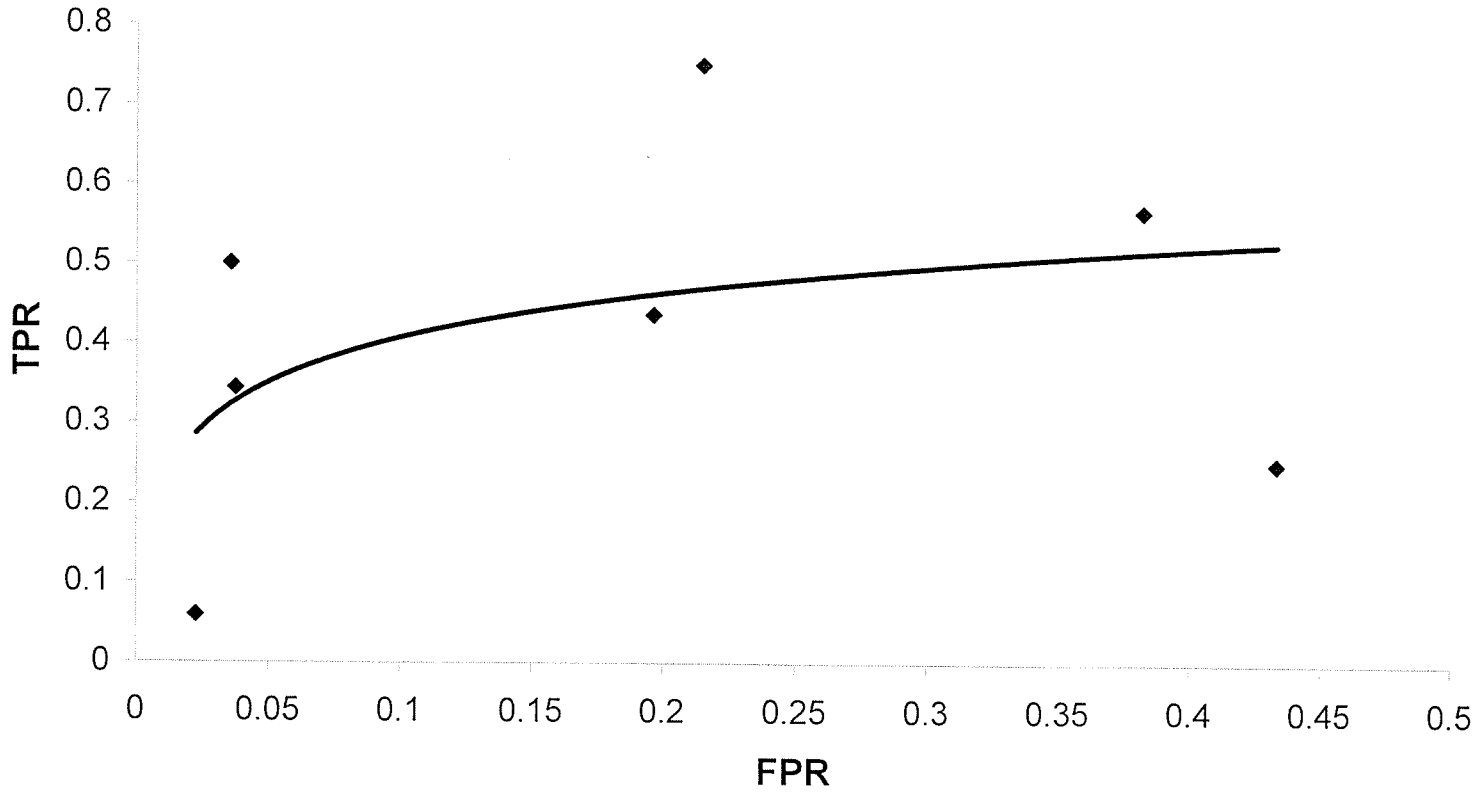

Figure 5.4

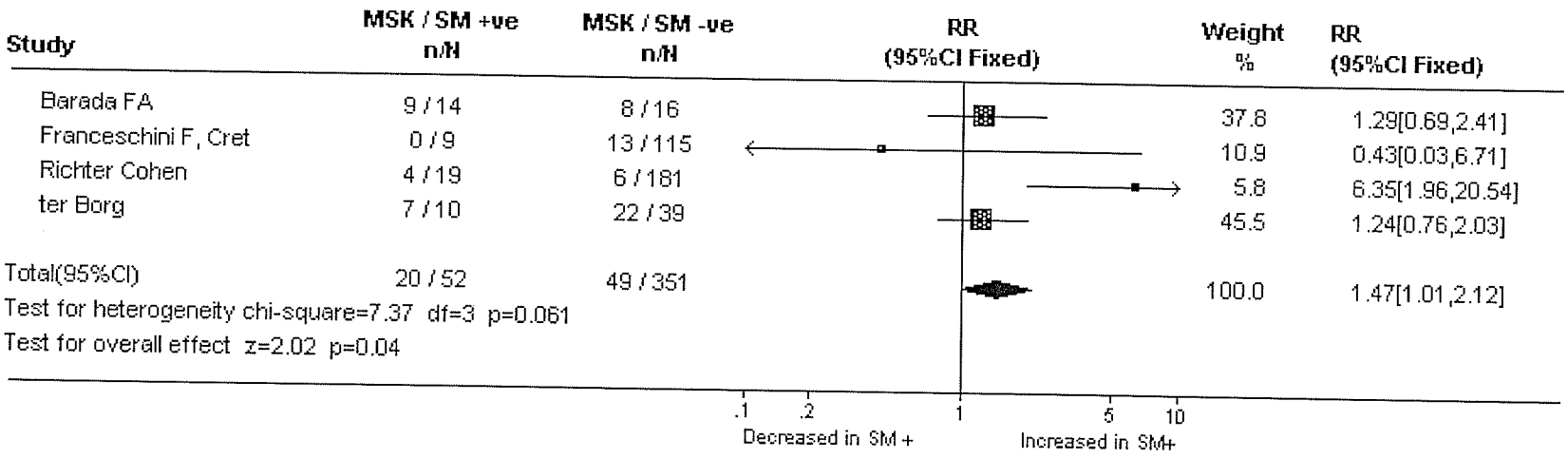
Study
MSK / SM +ve n/N
MSK / SM -ve n/N
RR (95%CI Fixed)
Weight %
RR (95%CI Fixed)
Barada FA 9 / 14 8 / 16 37.8 1.29[0.69,2.41]
Franceschini F, Cret 0 / 9 13 / 115 10.9 0.43[0.03,6.71]
Richter Cohen 4 / 19 6 / 181 5.8 6.35[1.96,20.54]
ter Borg 7 / 10 22 / 39 45.5 1.24[0.76,2.03]
Total(95%CI) 20 / 52 49 / 351 100.0 1.47[1.01,2.12]
Test for heterogeneity chi-square=7.37 df=3 p=0.061
Test for overall effect z=2.02 p=0.04
.1
.2
1
5
10
Decreased in SM+
Increased in SM+

Figure 5.5

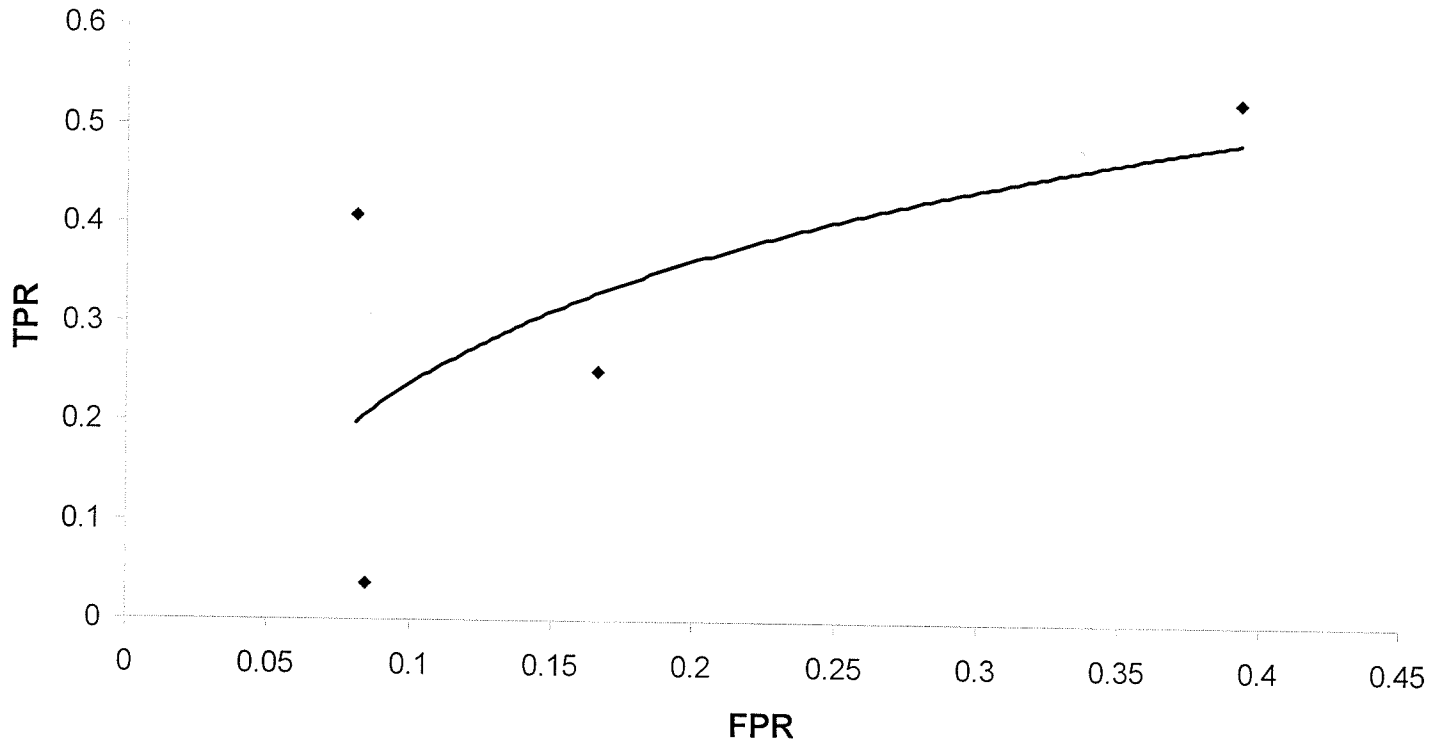

Figure 5.6

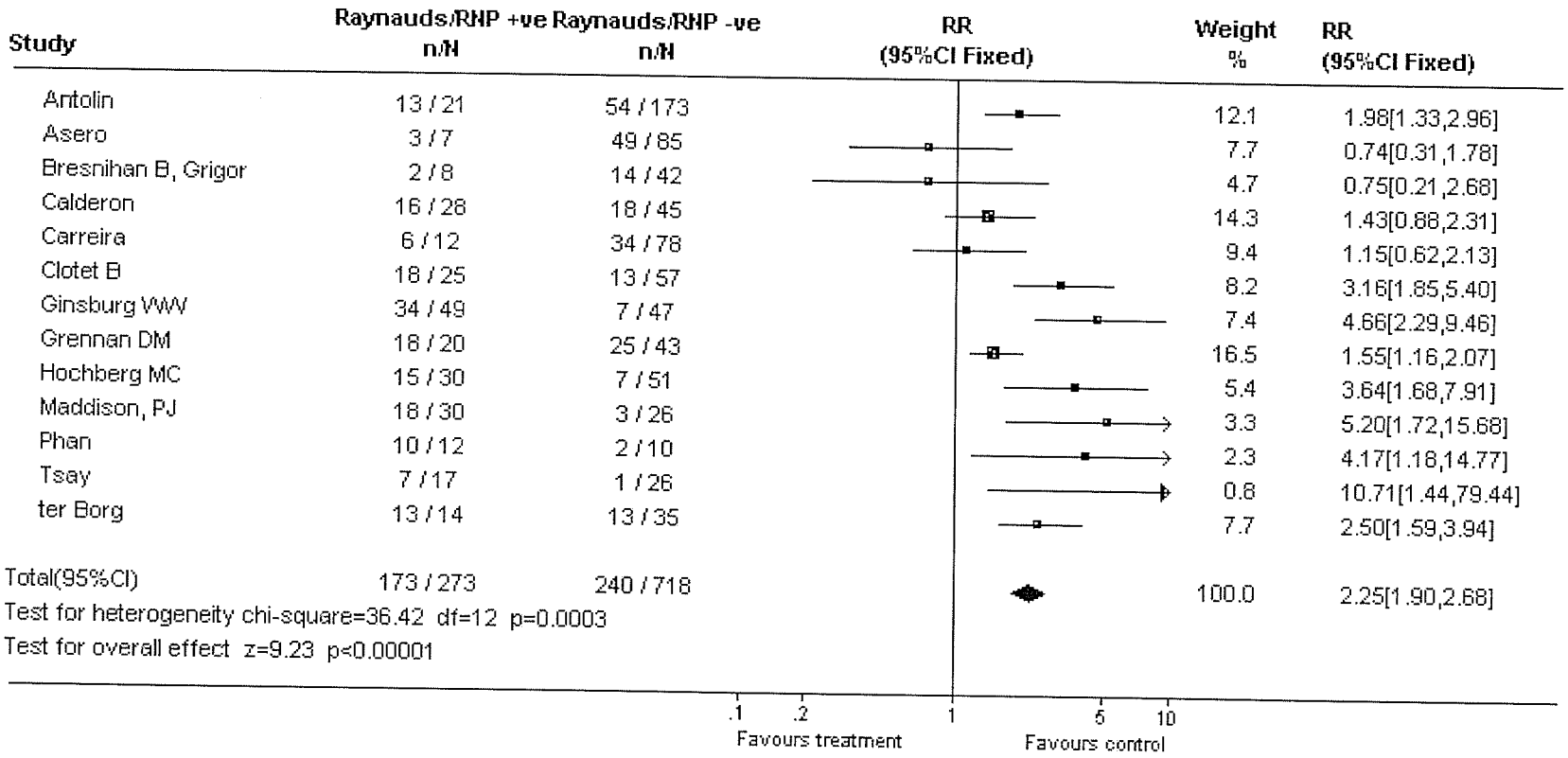
Study
Raynauds/RNP +ve n/N
Raynauds/RNP -ve n/N
RR (95%CI Fixed)
Weight %
RR (95%CI Fixed)
Antolin 13 / 21 54 / 173 12.1 1.98[1.33,2.96]
Asero 3 / 7 49 / 85 7.7 0.74[0.31,1.78]
Bresnihan B, Grigor 2 / 8 14 / 42 4.7 0.75[0.21,2.68]
Calderon 16 / 28 18 / 45 14.3 1.43[0.88,2.31]
Carreira 6 / 12 34 / 78 9.4 1.15[0.62,2.13]
Clotet B 18 / 25 13 / 57 8.2 3.16[1.85,5.40]
Ginsburg WW 34 / 49 7 / 47 7.4 4.66[2.29,9.46]
Grennan DM 18 / 20 25 / 43 16.5 1.55[1.16,2.07]
Hochberg MC 15 / 30 7 / 51 5.4 3.64[1.68,7.91]
Maddison, PJ 18 / 30 3 / 26 3.3 5.20[1.72,15.68]
Phan 10 / 12 2 / 10 2.3 4.17[1.18,14.77]
Tsay 7 / 17 1 / 26 0.8 10.71[1.44,79.44]
ter Borg 13 / 14 13 / 35 7.7 2.50[1.59,3.94]
Total(95%CI) 173 / 273 240 / 718 100.0 2.25[1.90,2.68]
Test for heterogeneity chi-square=36.42 df=12 p=0.0003
Test for overall effect z=9.23 p<0.00001
.1
.2
1
5
10
Favours treatment
Favours control

Figure 5.7

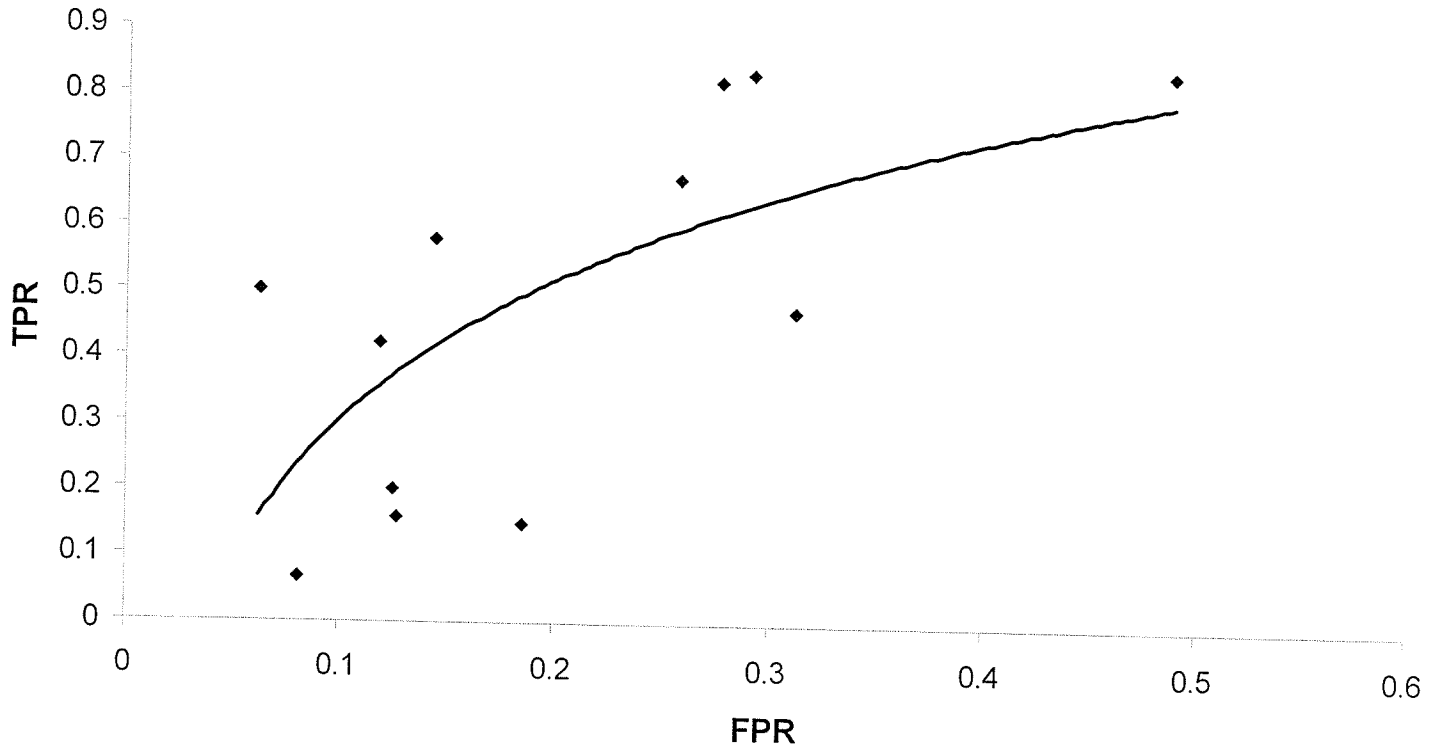

Figure 5.8

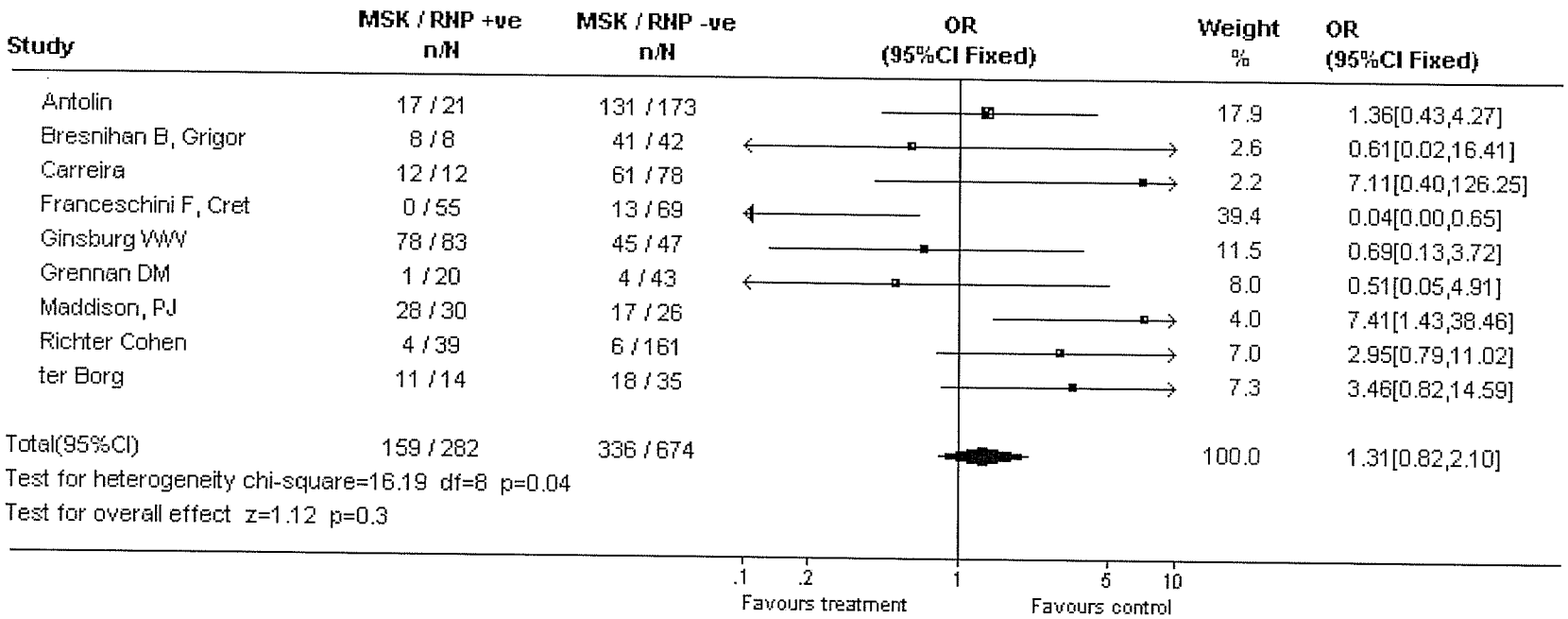

Figure 5.9a. (OR)

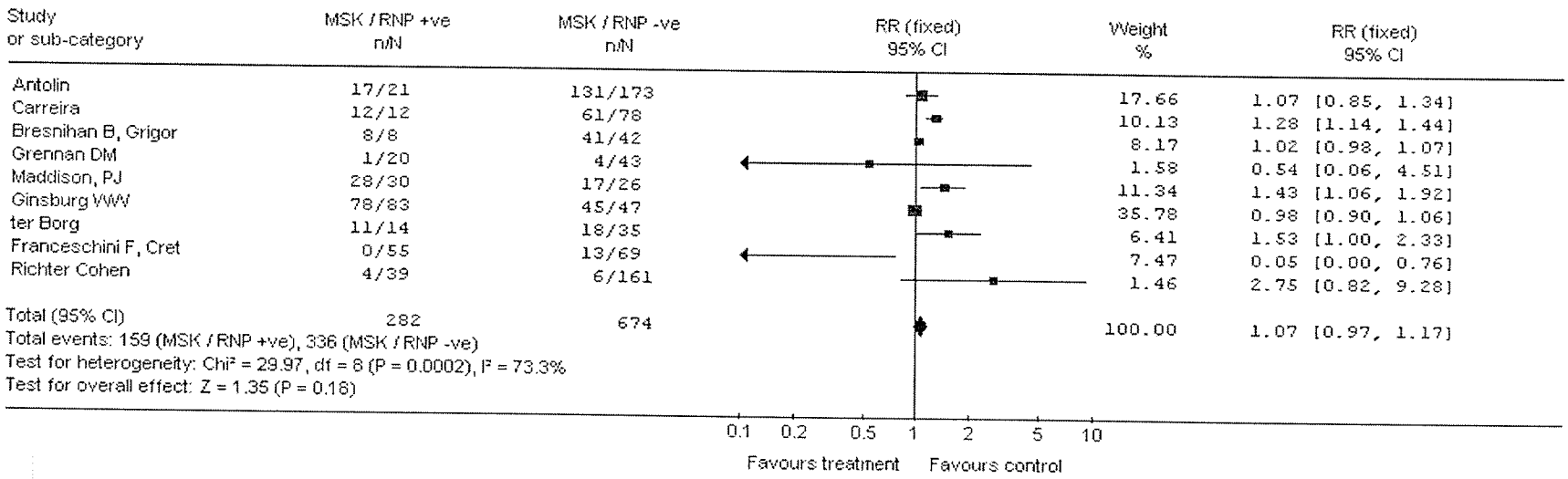

Figure 5.9b (RR)

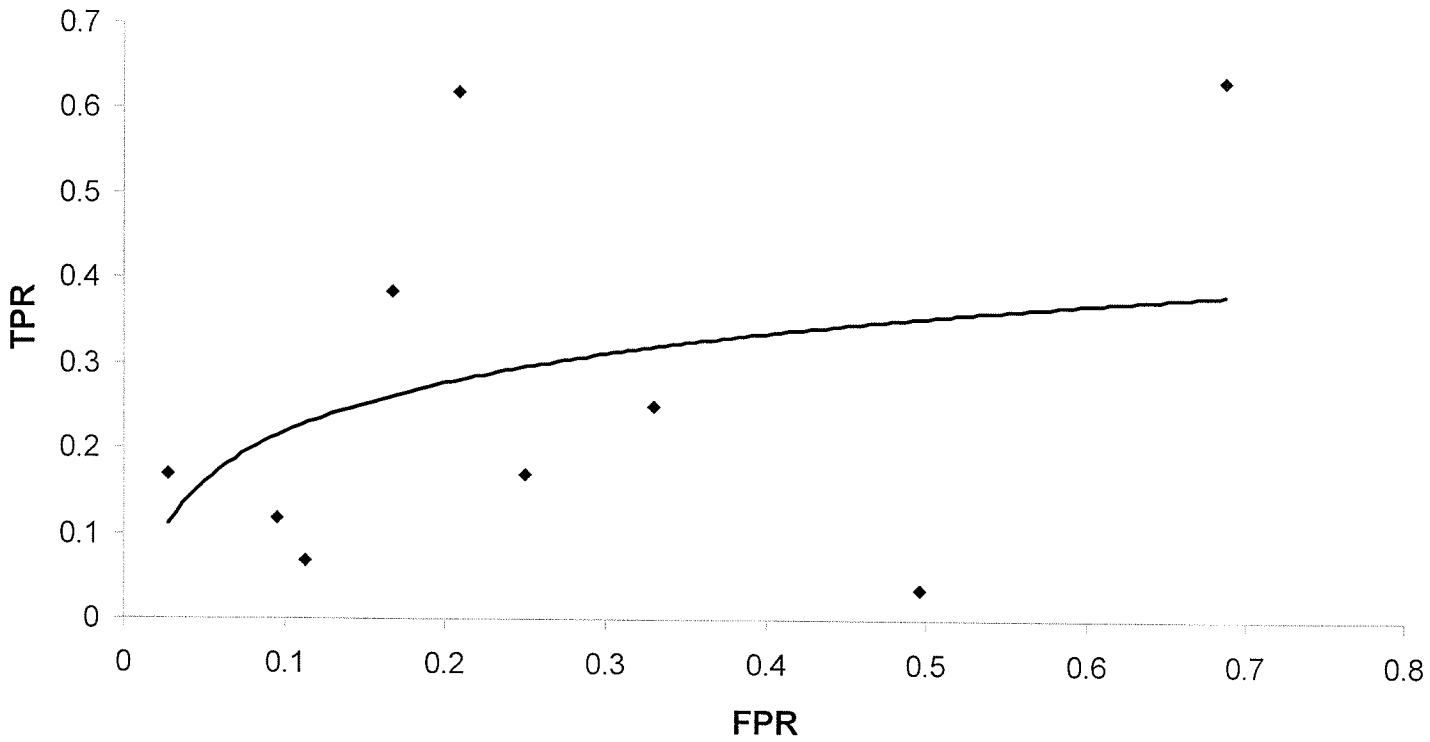

Figure 5.10

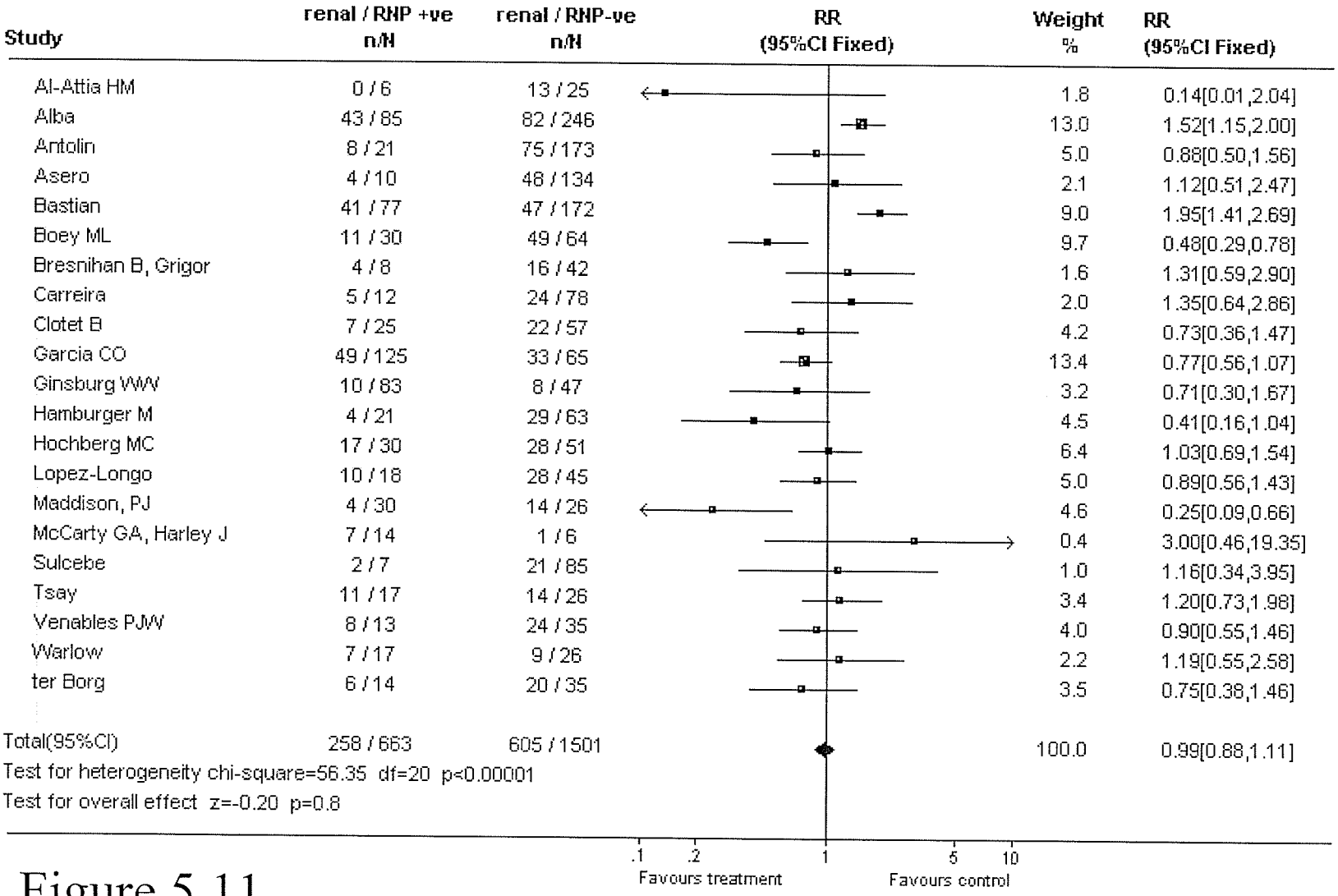
Study
renal / RNP +ve n/N
renal / RNP-ve n/N
RR (95%CI Fixed)
Weight %
RR (95%CI Fixed)
Al-Attia HM 0 / 6 13 / 25 1.8 0.14[0.01,2.04]
Alba 43 / 85 82 / 246 13.0 1.52[1.15,2.00]
Antolin 8 / 21 75 / 173 5.0 0.88[0.50,1.56]
Asero 4 / 10 48 / 134 2.1 1.12[0.51,2.47]
Bastian 41 / 77 47 / 172 9.0 1.95[1.41,2.69]
Boey ML 11 / 30 49 / 64 9.7 0.48[0.29,0.78]
Bresnihan B, Grigor 4 / 8 16 / 42 1.6 1.31[0.59,2.90]
Carreira 5 / 12 24 / 78 2.0 1.35[0.64,2.86]
Clotet B 7 / 25 22 / 57 4.2 0.73[0.36,1.47]
Garcia CO 49 / 125 33 / 65 13.4 0.77[0.56,1.07]
Ginsburg WW 10 / 83 8 / 47 3.2 0.71[0.30,1.67]
Hamburger M 4 / 21 29 / 63 4.5 0.41[0.16,1.04]
Hochberg MC 17 / 30 28 / 51 6.4 1.03[0.69,1.54]
Lopez-Longo 10 / 18 28 / 45 5.0 0.89[0.56,1.43]
Maddison, PJ 4 / 30 14 / 26 4.6 0.25[0.09,0.66]
McCarty GA, Harley J 7 / 14 1 / 6 0.4 3.00[0.46,19.35]
Sulcebe 2 / 7 21 / 85 1.0 1.16[0.34,3.95]
Tsay 11 / 17 14 / 26 3.4 1.20[0.73,1.98]
Venables PJW 8 / 13 24 / 35 4.0 0.90[0.55,1.46]
Warlow 7 / 17 9 / 26 2.2 1.19[0.55,2.58]
ter Borg 6 / 14 20 / 35 3.5 0.75[0.38,1.46]
Total(95%CI) 258 / 663 605 / 1501 100.0 0.99[0.88,1.11]
Test for heterogeneity chi-square=56.35 df=20 p<0.00001
Test for overall effect z=-0.20 p=0.8
.1
.2
1
5
10
Favours treatment
Favours control

Figure 5.11

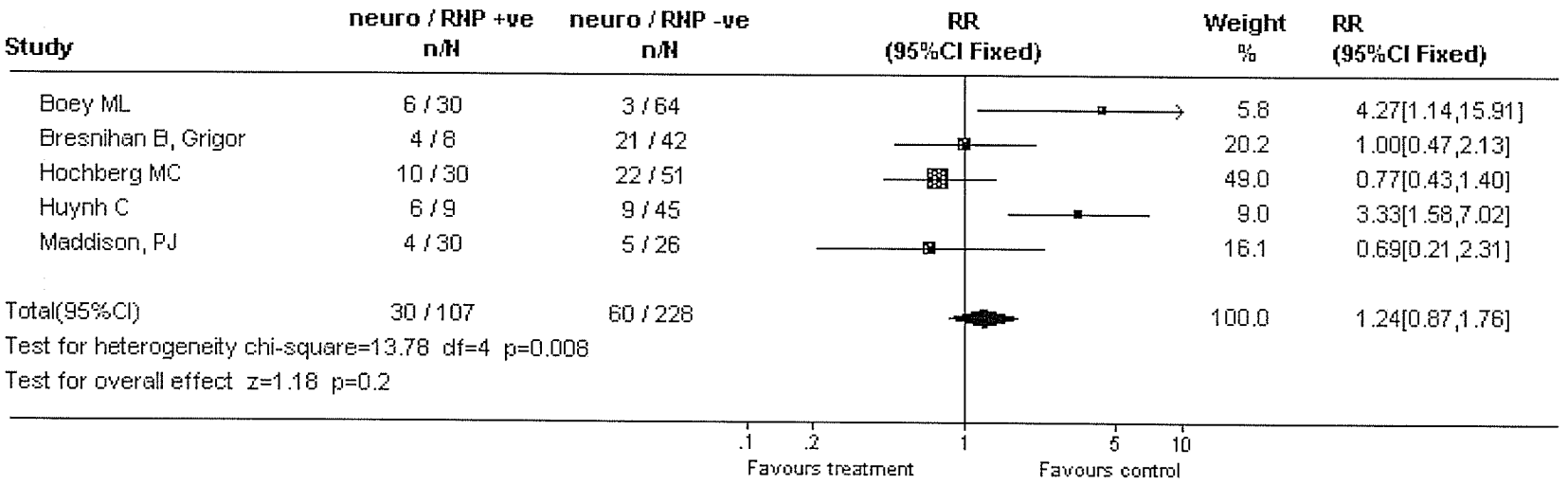
Study
neuro / RNP +ve n/N
neuro / RNP -ve n/N
RR (95%CI Fixed)
Weight %
RR (95%CI Fixed)
Boey ML 6 / 30 3 / 64 5.8 4.27[1.14,15.91]
Bresnihan B, Grigor 4 / 8 21 / 42 20.2 1.00[0.47,2.13]
Hochberg MC 10 / 30 22 / 51 49.0 0.77[0.43,1.40]
Huynh C 6 / 9 9 / 45 9.0 3.33[1.58,7.02]
Maddison, PJ 4 / 30 5 / 26 16.1 0.69[0.21,2.31]
Total(95%CI) 30 / 107 60 / 228 100.0 1.24[0.87,1.76]
Test for heterogeneity chi-square=13.78 df=4 p=0.008
Test for overall effect z=1.18 p=0.2
.1
.2
1
5
10
Favours treatment
Favours control

Figure 5.12

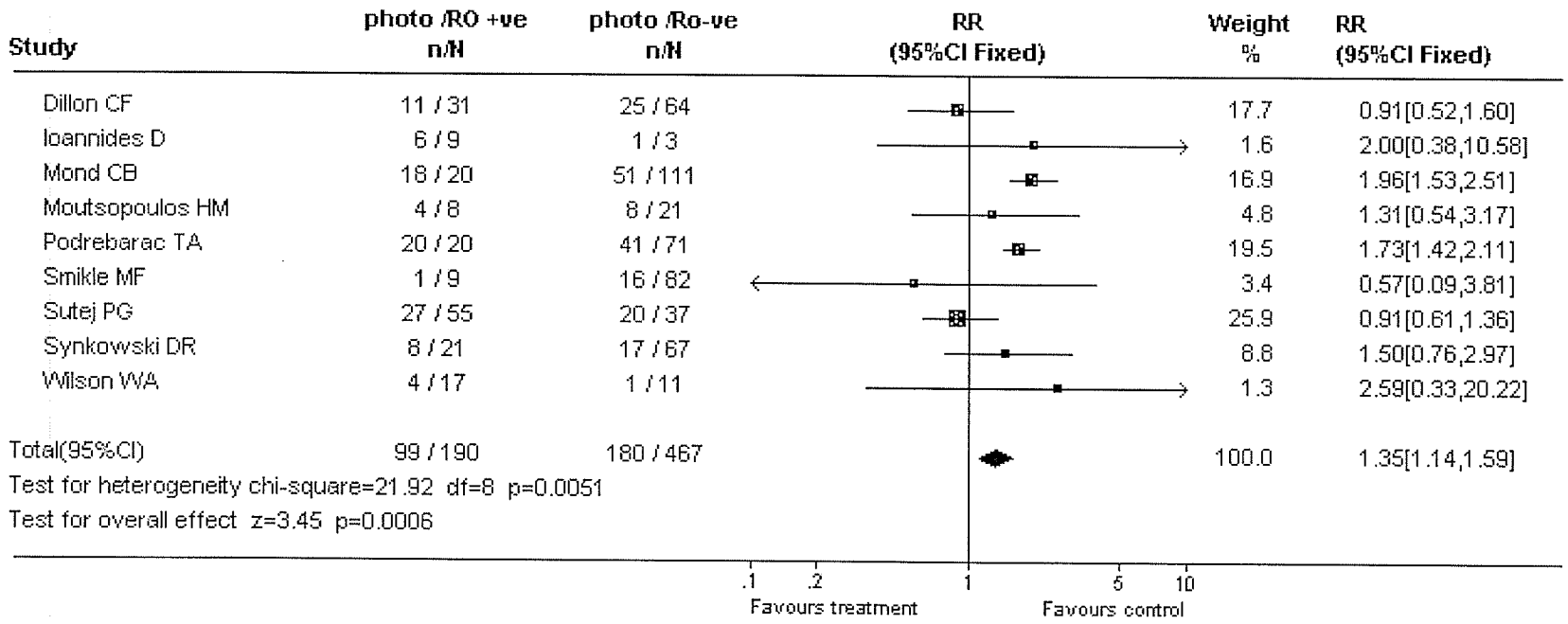
Study
photo /RO +ve n/N
photo /Ro-ve n/N
RR (95%CI Fixed)
Weight %
RR (95%CI Fixed)
Dillon CF 11 / 31 25 / 64 17.7 0.91[0.52,1.60]
Ioannides D 6 / 9 1 / 3 1.6 2.00[0.38,10.58]
Mond CB 18 / 20 51 / 111 16.9 1.96[1.53,2.51]
Moutsopoulos HM 4 / 8 8 / 21 4.8 1.31[0.54,3.17]
Podrebarac TA 20 / 20 41 / 71 19.5 1.73[1.42,2.11]
Smikle MF 1 / 9 16 / 82 3.4 0.57[0.09,3.81]
Sutej PG 27 / 55 20 / 37 25.9 0.91[0.61,1.36]
Synkowski DR 8 / 21 17 / 67 8.8 1.50[0.76,2.97]
Wilson WA 4 / 17 1 / 11 1.3 2.59[0.33,20.22]
Total(95%CI) 99 / 190 180 / 467 100.0 1.35[1.14,1.59]
Test for heterogeneity chi-square=21.92 df=8 p=0.0051
Test for overall effect z=3.45 p=0.0006
.1
.2
1
5
10
Favours treatment
Favours control

Figure 5.13

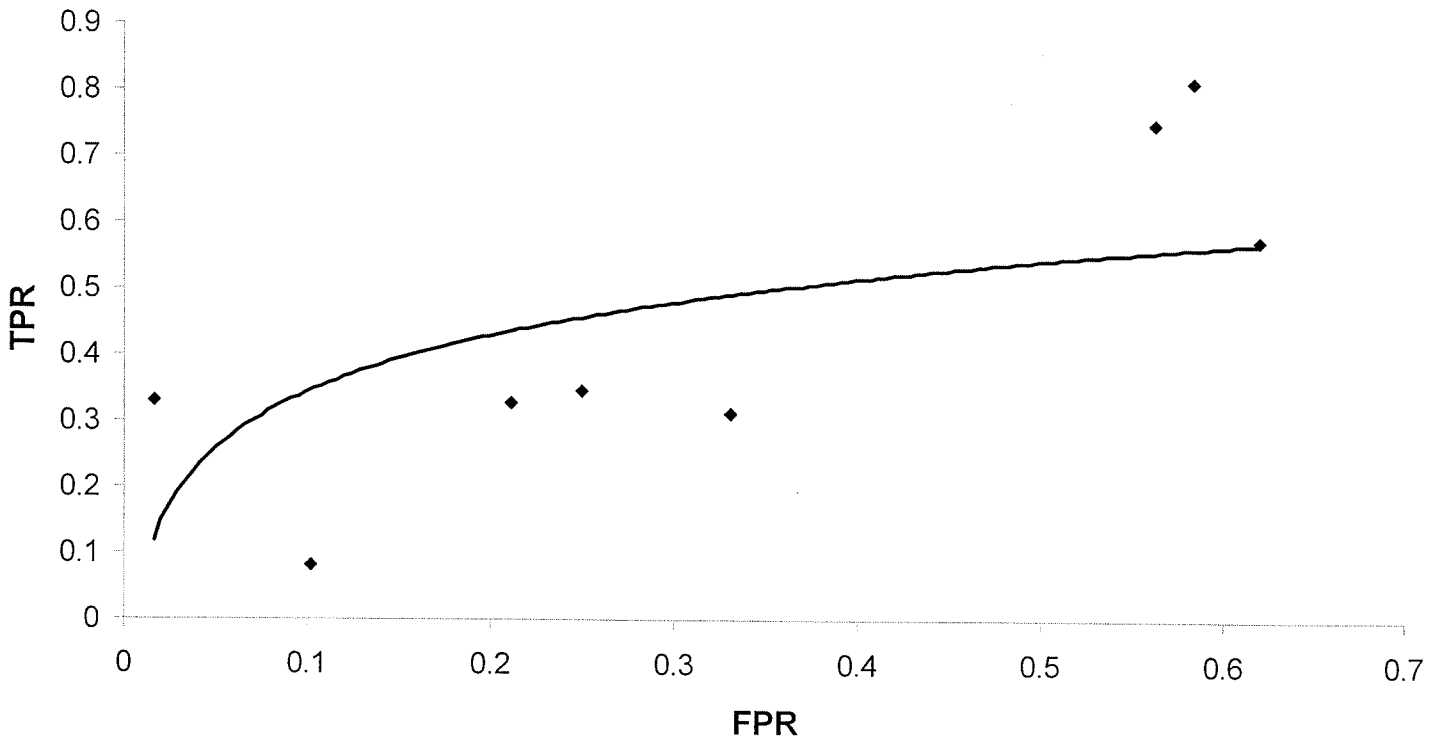

Figure 5.14

Appendix A

Search strategy for SLE and ENAs

("SLE" OR "systemic lupus erythematosus" OR "lupus" OR "lupus erythematosus,systemic [MESH]) AND ('ENA" OR "ENAs" OR "extractable nuclear antibod*" OR "extractable nuclear antigen" OR "RO" OR "Ro" OR "anti-Ro" OR "anti-RO" OR "anti-SSA" OR "anti-Ssa" OR "SSA" OR "Ssa" OR "LA" OR "La" OR "anti-La" OR "anti-LA" OR "SSB" OR "SSb" OR anti-SSB" OR "anti-SSb"

OR "SM" OR "anti-SM" OR "antiSM" OR "RNP" OR "ribonuclear protein" OR "anti-RNP" OR "SNRNP" OR "SnRNP"

OR "lupus anticoagulant" OR "anticoagulant*" OR "anti-coagulant*" OR "anticardiolipin*" OR "antiphospholipid*")

Appendix B

Calculations for determining the significance of sROC curves obtained from multiple studies (methods of Irwig and Moses)

FN = false negative
TN = true negative
TP = true positive
FP = false positive

$U = \text{Ln}\ [(FN + 0.5) / (TN + 0.5)]$

$V = \text{Ln}\ [(TP + 0.5) / (FP + 0.5)]$

$S = U + V$
$D = V - U$

S vs D plotted and linear regression line fit.
$(d = a + b\ s)$

$Q^* = 1/ [\{1 + \{\exp (b/-2)\}]$

Q^* ranges from 0.5 – 1.0
0.5= low accuracy
1.0 = high accuracy

CHAPTER 6

The presence of anti-SM antibodies is a stronger predictor of early mortality in the Manitoba Lupus population than ethnicity or socioeconomic status

To further explore the roles of ethnicity, socioeconomic status and autoantibody profile on SLE clinical features and outcome, a retrospective chart review of patients attending the University of Manitoba arthritis center and community clinics was performed. In this cohort, three ethnically distinct groups emerged which were available for study: Caucasians, First nations, and Asian-Orientals. Comparisons between these three groups provide a unique opportunity to evaluate the effects of genetics and ethnicity, socioeconomic status and autoantibody profile on lupus features and outcome. First Nations and Asian-Oriental patients are reported to have relatively high rates of renal and CNS involvement indicative of more severe lupus, yet differ significantly in socioeconomic status(13)(142). Caucasians and Asian Orientals in this cohort had similar and higher SES than First Nations, yet Caucasians generally had milder disease. SES does not influence access to health care in Canada, a potential concern with similar studies performed in countries without publicly funded health care.

In this study the presence of SM autoantibody was strongly predictive of early mortality when controlling for ethnic group and SES. Clinical associations between SM and RNP with renal disease were found and interestingly, an association of RNP and CNS disease. Low SES as measured by education levels and occupation scale was associated with greater end organ damage.

Methods

Patient identification

Patients with systemic lupus erythematosus (SLE) were initially identified as part of a previously reported prevalence study of lupus in Manitoba (14). The medical records of all practicing rheumatologists, nephrologists, hematologists and general internists and one oncologist known to have an interest in lupus were searched to identify patients diagnosed with lupus between 1980 and 1996 who met ACR inclusion criteria (99;100)(143). Two hundred and fifty nine (259) lupus patients were identified in this study and the medical records of 179 reviewed in detail. This was a known underestimation of all lupus cases in Manitoba based on a caregiver survey. An additional 93 patients with a diagnosis of systemic lupus erythematosus (SLE) attending the arthritis center between Jan 1 1996- Dec 31 2001 were subsequently identified through the Rheumatic Disease Unit (RDU) database. The charts of all newly identified patients were reviewed to confirm the diagnosis of SLE using established ACR criteria. Thus, the study period was from 1980-2001.

Clinical database

The RDU database was established in 1990 and contains demographic and clinical information on all patients attending the U of M arthritis center. Data is entered prospectively after the initial and each followup clinic visit. All patients give written informed consent to participate in database. Seven of the eight Manitoba rheumatologists and the one oncologist contributing patients to the initial prevalence study of lupus

maintained databases which facilitated identification of SLE patients in the initial study(14).

Clinical information collected

Demographic information (birth date, age at initial clinic visit, gender, self reported ethnicity, date of lupus diagnosis), and clinical manifestations of SLE were recorded. Ethnicity was recorded as Caucasian (C), Native American Indian (NAI) (includes treaty, and non-treaty status), Asian-Oriental (A), Asian-Indian, or African American. Métis were recorded as NAI or "other" depending on self report and only those recorded as NAI were analyzed. Treaty number confirmed treaty status for 25 (37%) of NAI. Thirty-one NAI (52%) were referred from nursing stations generally serving aboriginal communities.

Identification of specific clinical manifestations and end organ involvement of lupus were determined using ACR definitions (99;100). Renal involvement was recorded as ACR renal involvement (the presence of proteinuria (> 0.5 gm/d) or heme-granular / RBC casts or biopsy proven glomerulonephritis) and any renal involvement (proteinuria, hematuria, pyuria, biopsy proven glomerulonephritis, persistently elevated serum creatinine or ESRD). CNS involvement was recorded as ACR CNS involvement (seizures or psychosis) and any neurologic involvement (seizures, psychosis, CVA, cranial nerve or peripheral neuropathy, myelitis or cognitive impairment or lupus headache). Pulmonary involvement included pleuritis, pulmonary fibrosis, and pulmonary hypertension. Hematologic involvement included hemolytic anemia, leukopenia, lymphopenia, and thrombocytopenia.

Dermatologic involvement included SLE skin rash (malar or other), discoid lupus, alopecia, photosensitivity or skin vasculitis.

Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and the Systemic Lupus International Collaborating Clinic/ACR (SLICC/ACR)(36;44) scores were determined on patients where sufficient information could be extracted from the medical records. Mortality and date and cause of death if known were recorded.

Autoantibodies studied

Specific autoantibodies recorded were ANA, dsDNA, anti-SM, anti-RNP, anti-Ro, and anti-La. ANA titers were measured by immunofluorescence and ELISA, dsDNA by ELISA, and ENAs, anti-SM, RNP, Ro, and La, by immunoblot.

Socioeconomic status

Socioeconomic status was estimated in three ways. The number of years of formal education was recorded and analyzed as a continuous variable. Self-reported work status was recorded as employed full-time, employed part time, unemployed, retired, student, or disabled and provided a proxy measure of actual financial income. Occupational prestige was measured using the British Census Scale (BCS). The British census scale categorizes occupations and levels of occupational responsibility into 5 categories. Categories 1 includes professionals, category II includes mangers and non-professional occupations, category III includes skilled occupations, both manual and non-manual, category IV includes partly skilled workers and category V includes non-skilled workers. Students (and

homemakers) were classified in category III. Occupation was recorded by 43% of the cohort. The BCS has previously been used to measure SES of lupus patients (27). Work status and occupational prestige were used as a proxy for financial income.

Statistical methods used

Univariate analysis was performed using Chi squared, student T tests and non-parametric tests (Mann-Whitney U) or Fischer's Exact test as appropriate. Correlations were performed using Pearson or Spearman rho correlation coefficients as appropriate. Statistical significance was determined as $p<0.05$.

Multivariate analysis to identify predictors of SLICC scores was performed using linear regression. Included variables were identified by univariate analysis. Variables were entered into the regression analysis using an F probability of 0.05, and removed using an F probability of 0.10. Both the entry and stepwise methods were used with similar results.

Variables affecting survival (mortality) with time variables defined as duration of disease after diagnosis or age at last clinic visit were analyzed using Kaplan Meier survival curves and Log Rank statistics. Cox's proportional hazards regression analysis was used to determine the relative influence of demographics and clinical features in determining survival. Continuous and categorical variables were identified and entered into the model using $p=0.05$ and removed using $p=0.10$ with a maximum of 20 iterations. Both the entry and forward conditional likelihood ratios are reported.

Results

Demographic, clinical and socioeconomic status description of cohort

The current study population consists of 259 lupus patients identified in a previously reported prevalence study of lupus in Manitoba (14) and an additional 93 patients. All patients met ACR criteria for SLE. The demographics, clinical features and socioeconomic status of the patients are presented in Table 6.1. The cohort consisted primarily of Caucasians (68%). Other ethnic groups represented included NAI (19.3%), Asian-0riental (6%), Asian-Indian (2.3%) and African-American (2.3%). Ethnicity was not recorded by 2.2% of the cohort. Ethnic comparisons were made only between Caucasians, NAI and Asian-Orientals due to the small numbers in other ethnic groups.

Clinical features

Asian-Orientals and NAI patients were diagnosed with SLE at an earlier age than Caucasians (28.2, 31.5 vs 36.3 $p<0.002$). The delay to diagnosis from symptom onset was shortest for Asian-Orientals (4 ± 5 months, vs 27.4 ± 38 for Caucasians and 27.9 ± 39 months for NAI $p<0.001$); however, there were no differences in duration of follow-up. The majority of patients were female and there were no differences in gender ratios between ethnic groups.

Renal disease was more prevalent in NAI and Asian-Orientals than in Caucasians. This was true for renal involvement meeting strict ACR criteria (proteinuria and casts) (57% and 63% vs 32 % $p< 0.009$) and for the presence of any renal disease or damage (56% and 74% vs 31% $p<0.003$). Neurologic involvement (seizures or psychosis) was higher in Asian-

Orientals than NAI (37% vs 13 p<0.012) or Caucasians (9% p<00001). However, when all neurologic involvement, including headaches and stroke were compared, the difference between Asian-Orientals and Caucasians and NAI was much less (37% vs 19%, 23% p<0.06). Pulmonary involvement was also highest in Asian-Orientals (53% vs 34 %-NAI and 27 % Caucasian p<0.029). No differences were seen in hematologic or dermatologic involvement.

Ethnic differences in individual clinical diagnostic criteria of SLE and other clinical features are shown in Table 6.2. The main ethnic differences were seen in specific renal and CNS features. Asians were more likely to have myositis, and Caucasians were least likely to have vasculitis, fever, or reduced complement levels.

SLICC and mortality

The degree of end organ damage due to SLE was measured using SLICC scores (Table 6.3). SLICC scores were available at diagnosis on 196 (60%) patients, 168 (51%) at 2 years, and 283 (86%) patients at last visit. At diagnosis, SLICC scores were similar between the three ethnic groups however, at 2 years, Asians and NAIs had higher SLICC scores than Caucasians. At last visit, SLICC scores differed between the ethnic groups (p=0.04) and were highest in NAI and lowest in Caucasians (p<0.003 NAI vs Caucasian). This was primarily due to increased renal damage and to a lesser extent, increased pulmonary damage. SLICC scores in Asians (1.61) at last visit were statistically similar to Caucasians and NAI.

Overall mortality in the cohort was 7.6% (26 deaths). NAI had the highest mortality (13.2% vs 5.8% and 9.1 % for Caucasians and Asians $p<0.04$). Although the cause of death was not known for the majority of subjects, patients who died were more likely to have had renal involvement (proteinuria or casts) $p<0.005$). The age and disease duration at the time of death are shown in Figure 6.1. Peak ages of death were between ages 30-40 and 60-70 years. Disease duration at the time of death was less than 10 years for the majority of patients.

These clinical profiles support previous data which suggest NAI and Asian Orientals have a more severe and potentially more aggressive form SLE compared to Caucasians with earlier onset, greater renal and CNS involvement and more end organ damage as reflected in higher SLICC scores. However, despite similar clinical severity to Asian Orientals, NAI had the highest overall mortality.

Clinical associations with antibodies to extractable nuclear antigens (ENAs)

Associations between specific antibodies to extractable nuclear antigens (ENAs) and selective features of SLE have been described previously. In particular, SM has been associated with renal disease and Ro with skin involvement. Differences in the ENA profiles between the three ethnic groups could contribute to differences seen in clinical features and outcomes. We determined the clinical associations of individual and combinations of ENAs and compared ethnic differences in ENA profiles. Extractable nuclear antigens were measured in 216 patients (62%). There were no statistically

significant differences in whether ENA testing was performed among the different ethnic groups (Table 1) or with specific clinical features of the patients (Table 6.4).

SM/RNP

As previously described, SM antibodies were associated with renal involvement (any renal $p<0.006$; ACR renal criteria-proteinuria or casts $p< 0.002$) and interestingly, also with CNS involvement (any CNS $p<=0.001$; ACR CNS criteria- seizures or psychosis $p<0.0001$) (Table 6.4). In particular SM antibodies were highly associated with proteinuria ($p<0.003$), renal casts ($p<0.04$), seizures ($p<0.0001$), psychosis ($p<0.0001$), lymphopenia ($p<0.03$), organic brain syndrome ($p<0.06$), vasculitis ($p<0.014$) and fever ($p<0.019$). RNP antibodies were also associated with ACR renal involvement ($p<0.026$) and ACR neuro involvement-seizures or psychosis ($p<0.001$). RNP antibodies were associated with psychosis and to a lesser degree with proteinuria ($p<0.021$), lymphopenia ($p<0.015$) and vasculitis ($p<0.07$), alopecia ($p<0.03$), and leukopenia ($p<0.04$). The presence of both SM and RNP antibodies did not increase the risk of renal or CNS involvement (Table 6.5). The sensitivity and specificity of SM and RNP for renal and neurologic disease in this cohort are shown in Table 6.6 and are similar to values reported in the literature.

Ro/La

Ro was associated with low complement levels ($p<0.04$), and hematologic features ($p<0.05$) in particular leukopenia ($p< 0.06$) and lymphopenia ($p<0.02$). La was associated with lymphopenia ($p< 0.02$) and vasculitis ($p<0.07$). No associations with dermatologic or

pulmonary features were seen. Combinations of ENAs did not increase the risk of developing individual clinical features. (Table 6.5).

Outcome measure associations with ENAs

Extractable nuclear antigens were measured in over 60% of the cohort. Those who had ENAs measured had shorter disease duration (9.1 vs 10.7 years $p< 0.0001$) likely reflecting changing clinical practice patterns. As a result, patients with ENAs measured generally had lower SLICC scores (at the last visit) ($p<0.03$) thus any identified associations with organ damage may be underestimated. Despite this, RNP antibodies, but not SM antibodies, were associated with greater end organ damage as reflected by higher SLICC scores (1.71 vs 1.01 $p<0.004$). Importantly, the presence of SM but not RNP autoantibodies was significantly associated with mortality ($p<0.03$ Fischer's exact test). Ro and La antibodies were not associated with SLICC scores or mortality.

Ethnic associations with ENAs

NAI and Asian-Orientals had a higher frequency of both SM ($p<0.0001$) and RNP autoantibodies ($p<0.0001$) than Caucasians (Table 6.1) potentially explaining their higher degree of renal and neurological involvement. No differences were seen in Ro or La positivity between the three ethnic groups.

Socioeconomic status

NAI and Asian Orientals were equally likely to have SM antibodies which were seen to be associated with mortality, however, only NAI had a much higher mortality rate suggesting

other factors influence disease outcome, in particular mortality, in this lupus cohort. Socioeconomic status (SES) is known to have an important influence on the outcome of chronic disease and higher SES is associated with better indicators of health outcome. Years of formal school education was used as a surrogate marker of SES and recorded for 259 (73.8%) patients (Table 6.1). Self-described work status, either full time, part time, retired, disabled, or unemployed was available on 267 patients. Socioeconomic status was also measured using the British Census Scale (BCS) in 150 (42.7%) subjects on whom occupational information was available. The British census scale categorizes occupations and levels of occupational responsibility into 5 categories.

There were no differences in the reporting of education, occupation, or work status between the three ethnic groups (Table 6.1). Caucasians and Asian-Orientals had similar levels of schooling (13.2 vs 13.5 p=ns) and both had more schooling than NAI (10.1 yrs $p<0.0001$). Self reported work status also reflects SES and NAIs were less likely to be employed ($p<0.004$) than Caucasians or Asian-Orientals however there were no significant differences in self-reported disability. Socioeconomic status as measured by the BC scale further confirmed higher SES in Caucasians (2.8) and Asians (3.1) compared to NAI (3.3 $p<0.005$). The differences between Asians and NAI (p=ns) and Asians and Caucasians (p=ns) were less striking.

Clinical associations with socioeconomic status

Socioeconomic status and clinical features were ascertained retrospectively and it is not possible to determine the temporal relationship between the two in this study; however,

patients with renal disease (proteinuria or casts) had fewer years of education (12.1 vs 12.9 $p<0.05$) and were less likely to be working ($p<0.001$). Patients with any neurologic involvement were also less likely to be working, ($p<0.038$), had higher BC scores (3.3 vs 2.8 $p<0.003$), and in particular, were less likely to be working in managerial positions ($p<0.005$ Fischer's).

Lower SES was also associated with greater disease damage. SLICC scores were negatively correlated with years of schooling, progressively increased with increasing tertile of the BCS (ie with decreasing socioeconomic status) and were higher in patients who were not working. Mortality was not correlated with education level, BCS nor work status.

Thus, SES is lower in patients with more severe disease; however, socioeconomic status, as determined by occupation, work status, or education, was not measured at the onset of disease and thus it is not possible to determine if disease adversely affected attained socioeconomic status or whether poor socioeconomic status influenced disease severity.

SLE outcome multivariate analysis

Predictors of SLICC at last clinic visit

Multivariate analysis was used to determine the influence of ethnicity, SES and autoantibody status on SLICC scores at last visit while controlling for disease duration. SLICC scores at last visit were predicted by anti-RNP positivity, education, and duration of follow-up (Table 6.7).

Predictors of mortality

Kaplan Meier survival curves based on ethnicity, autoantibody status and renal or CNS involvement are shown in Figures 6.2 and 6.3. Survival (age of death) was significantly affected by ethnicity (16.1 $p<0.0001$, anti SM positivity (20.5 $p<0.00001$), ACR renal disease (10.1 $p<0.002$) or any renal disease (Log Rank 3.23 $p<0.07$). RNP positivity, neurologic involvement and socioeconomic status did not affect survival. Similar results were obtained for survival after diagnosis (disease duration) (Ethnicity (Log Rank 6.0 $p<0.05$)) (SM positive (Log Rank 15.7 $p<0.0001$), ACR renal disease (Log Rank 5.3 $p<0.02$), or any renal disease (Log Rank 4.0 $p<0.05$).

Cox proportional hazards regression analysis was performed to determine the effects ethnicity, autoantibody status, organ involvement and damage, and socioeconomic status as measured by education, work status or occupational prestige scale on overall mortality. Initial binary logistic regression testing identified anti-SM antibody (OR 4.6 (1.3-16.3)$p=0.02$), NAI ethnicity (OR 2.4 (1-5.7) $p=0.05$), the presence of ACR defined renal lupus (OR 4.2(1.4-12.2) $p=0.009$), and the final SLICC score (OR1.5 (1.2-1.8) $p<0.001$) as the only individual predictors of overall mortality in this cohort. Socioeconomic status, whether measured by education, work status or occupational index, did not contribute significantly to overall mortality. Further Cox proportional hazards regression analysis was performed to determine the relative influence of ethnicity, education, and autoantibody status on survival (disease duration after diagnosis), while controlling for age at last visit, gender and disease severity (SLICC) at last visit (Table 6.8). Anti-SM antibody (OR 0.02

(0.001-0.6)) and age at last visit (OR 1.1(1-1.2) were the only predictors of early death (model Chi square 20.7 p=0.004)) using a full entry model. Only SM positivity contributed to reduced survival after diagnosis in the forward conditional model (OR of survival 0.08 (0.01-0.5) model Chi square 11.3 p<0.001). Importantly, SES when measured by education, work status or occupational prestige (BC scale) did not contribute significantly to reduced disease duration (early mortality) after controlling for disease severity. Similar analysis to determine the effects of ethnicity, education, and SM positivity on age at death, while controlling for gender and disease duration also indicated that only anti-SM antibody was predictive of poorer survival after diagnosis using forward conditional models (OR of survival 0.08 (0.01-0.5) model Chi square 10.9 p=0.001). Treatment data was available on a proportion of the cohort (54%) but did not influence survival when included in the model.

Inclusion of renal involvement into either model using forward likelihood ratios negated the influence of SM. This suggests that the strong predictive value of SM relates to it being a primary risk factor for severe renal involvement, thereby influencing mortality. Ethnicity was initially a significant predictor of early mortality, but inclusion of SM or renal involvement into the model negated the effect of ethnicity. This suggests that the poor survival seen in some ethnic groups relates, in part to, SM positivity. Cox's proportional hazards regression models including ethnicity, education, SM positivity and renal damage as measured by the renal component of the SLICC while controlling for gender, indicated both SM and renal SLICC predicted early mortality after SLE diagnosis.

Discussion

In this cohort, three ethnically distinct groups emerged which were available for study: Caucasians, Native American Indians, and Asian-Orientals. Comparisons between these three groups provide a unique opportunity to evaluate the effects of ethnicity, socioeconomic status and autoantibody profile on lupus features and outcome. The severity of SLE varies between the ethnic groups. The First Nations and Asian-Oriental patients studied had relatively high rates of renal and CNS involvement indicative of more severe lupus and also had an increased frequency of anti-SM and anti- RNP autoantibodies which is consistent with previous reports of more severe disease in populations with these autoantibodies. However, despite similar disease severity, overall mortality was higher in First Nations than Asians.

The strongest predictor of mortality in this study was the presence of anti-SM autoantibody and to a lesser extent the degree of end organ damage, especially renal. This may relate to the strong association of SM with renal disease as those who died were more likely to have renal disease and possibly also other complications associated with renal disease. Other factors not measured likely contribute to mortality since Asians, who have a high degree of SM positivity had comparable mortality to Caucasians. Diabetes, cardiovascular disease and injury related mortality rates are high in the aboriginal population and were not measured in this study. Factors influencing the development of anti-SM are still unknown although several genetic haplotype associations have been reported and as with other autoantibodies, defective clearance of apoptotic cells may contribute to activation of anti-SM producing B cells (143).

Clinical associations with individual autoantibodies have been widely reported and the association of SM and renal involvement seen here is consistent with other reports. The association of RNP with renal disease is less clear with some reports even suggesting a protective effect of RNP on renal lupus (26, 32). In this study RNP was positively associated with renal disease. This discrepancy may be partly due to limited sample size. Interestingly, in addition to an association RNP with renal involvement we found RNP was associated with CNS involvement in particular seizures, and importantly organ damage (SLICC).

SES differed between the three ethnic groups and contributed to the degree of organ damage as measured by the SLICC score at the last clinic visit but was not a contributor to early mortality. The association of SES and damage is consistent with previous studies (19;22;40) although the extent to which the morbidity associated with organ damage contributes to low SES either due to difficulties obtaining education or employment compared to the influences of low SES contributing to organ damage is still unclear. Given that organ damage contributes to mortality, interventions directed to improving SES in the lupus population may improve clinical outcome.

The lack of direct association between SES and mortality differs from most previous studies (29;30;33-35;47). Health care is publicly funded in Canada and thus financial barriers should have less influence on health care provision than in countries which rely on a payer based system for health care. Previous studies of SES in lupus outcomes have been

primarily performed in the USA where lack of insurance potentially limits health care access. Non-financial factors associated with lower SES such as attitudes to health related behaviors are difficult to assess and were not measured in the current study however, may have affected the results (26). Geographic isolation remains a potential limitation of the study however, travel for medical reasons is subsidized for First Nations patients who form the largest section of the cohort traveling extended distances.

Ethnicity in this study was determined by self report without detailed questioning of parental heritage or specific genetic admixture testing. Over time, the Manitoba population is becoming increasingly a mosaic of genetic backgrounds. Previous studies of relatively homogenous population groups have demonstrated significant mixed genetic ancestry and it is likely that the ethnic groups studied here also have a variable degree of mixed ancestry. This genetic admixture, in particular the contribution of Amerindian genes may be an important contributor to clinical disease activity in lupus (16;21). A more detailed genetic analysis would be needed to determine the specific genetic influences in this cohort.

Ethnicity also relates to cultural behaviors and attitudes. The contribution of environmental influences such as dietary practices, cultural practices, use of complementary therapies, or attitudes to health care were not measured but are also potentially important variables affecting lupus activity and subsequent damage.

The study findings may have been affected by sampling, information and ascertainment bias. Although the cohort studied is representative of lupus patients seen by rheumatology

specialists in Manitoba, there is significant under-referral of patients with potentially milder disease (Peschken, unpublished observations) and the majority of the cohort was followed in an academic lupus clinic and may not be representative of community practice. The clinical information was obtained by retrospective chart reviews and in some cases full demographic and clinical data could not be extracted or was not provided by the subjects. Mortality is likely under-reported as extended follow-up was not available on all patients. In addition, cause of death was not known and thus lupus related mortality couldn't be determined. These sources of sampling, information and ascertainment bias are best addressed by a prospective study including patients followed both in community and academic clinics in which there is detailed data collection of both clinical variables and demographics, especially ethnicity and admixtures, socioeconomic status variables.

Identifying prognostic features early in the course of disease assists clinicians in stratifying patients for monitoring and therapeutic options. While the evidence for ENA and clinical associations is not yet strong enough to influence changes in therapy based solely on ENA testing, the presence of SM or RNP autoantibodies should prompt continued vigilance in monitoring for serious organ involvement in particular renal and CNS. In addition, more attention needs to be given towards addressing socioeconomic concerns in the management of patients with SLE.

Acknowledgments

Dr. Taback for helpful discussions concerning the meta-analysis. The patients and rheumatologists Arthritis Center allowed access to clinic records. The University of Manitoba and Health Sciences Center Foundation assisted with funding.

Table and Figure legends

Table 6.1. Demographic and clinical features of SLE cohort.

†NAI vs Caucasian + Asians p<0.01; ‡ NAI vs Caucasians + Asians p<0.0001

Caucasian vs NAI + Asians p<0.001; $ Caucasian vs NAI + Asians p<0.0001; £C vs N+A p<0.01; * Asian vs NAI p<0.01 ; **Asian vs NAI p<0.001; ;@ Asian vs Caucasian p<0.05; @@@Asian vs Caucasian p<0.01; @@ Asian vs Caucasian p<0.0001; § Asian vs Caucasian p<0.05; §§ Asian vs NAI+ Caucasian p<0.001; §§§ Asian vs NAI + Caucasian p<0.0001

Table 6.2 Frequency of clinical features in Caucasians, Asian and NAI with SLE numbers represent % of patients with clinical feature

¶ includes arthralgias

† NAI vs Caucasians + Asian p<0.05; ††NAI vs Caucasian + Asians p<0.01; ‡ Caucasians vs NAI+ Asians p<0.05

£C vs N+A p<0.01; # Caucasian vs NAI + Asians p<0.001; * Asian vs NAI p<0.01; @ Asian vs Caucasian p<0.05; @@Asian vs Caucasian p<0.01; @@ @Asian vs Caucasian p<0.001; § Asian vs Caucasian p<0.0001; $ Asians vs NAI + Caucasian p<0.01; §§ Asian vs NAI+ Caucasian p<0.05; & Fischer's exact

Table 6.3. Proportion of patients with renal or CNS involvement testing positive for ENAs including all ethnicities. All values reported as number with +ve antibody/number with

condition tested for antibody (%). *p< or = 0.05; + p<0.01; # p< or = 0.001; @ Fishers exact test

Table 6.4 Clinical outcome of ethnic groups with SLE

† NAI vs Caucasian + Asians p<0.05;††NAI vs Caucasian + Asians p<0.01;‡ NAI vs Caucasians + Asians p<0.0001;†† NAI vs Caucasian + Asians p<0.05;

Caucasian vs NAI + Asians p<0.05, ## Caucasians vs NAI + Asians p<0.01

Table 6.5 Proportion of patients with selective clinical features testing positive for ENAs including all ethnicities. All values are reported as the number of patients positive for the antibody per the number of patients with the clinical feature tested for the antibody (%).

* p< or = 0.05; + p<0.01; # p<0.001; @Fishers exact test.

Table 6.6 Sensitivity and specificity of SM and RNP with renal and neurologic disease

Table 6.7 Predictors of SLICC at last clinic visit a) Enter method b) Step-wise method

Table 6.8 Predictors of survival using Cox regression analysis

a) Disease duration enter method and forward conditional likelihood ratios
b) Age of last clinic visit forward conditional likelihood ratios
c) Proportional hazards of disease duration (survival after diagnosis)

Figure 6.1 Age and disease duration at the time of death

a) Age of death

b) Disease duration at time of death

Figure 6.2 Kaplan-Meier survival curves of age at last visit

a. ethnicity; b. anti-SM positivity; c, any renal disease; d ACR renal disease (proteinuria or casts)

Figure 6.3 Kaplan-Meier survival curves of disease duration

a. ethnicity; b. anti-SM positivity; c, any renal disease; d ACR renal disease (proteinuria or casts)

Table 6.1 Demographic and clinical features of SLE cohort.

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Caucasian vs NAI + Asians p<0.001; $ Caucasian vs NAI + Asians p<0.0001; £C vs N+A p<0.01; * Asian vs NAI p<0.01 ; **Asian vs NAI p<0.001; ;@ Asian vs Caucasian p<0.05; @@@Asian vs Caucasian p<0.01; @@ Asian vs Caucasian p<0.0001; § Asian vs Caucasian p<0.05; §§ Asian vs NAI+ Caucasian p<0.001; §§§ Asian vs NAI + Caucasian p<0.0001

	Caucasian	*Asian*	*NAI*	*AI*	*AA*
Demographics					
N (%)	240 (68%)	22 (6%)	68 (19.3%)	8 (2.3%)	8 (2.3%)
Gender (% female)	89	91	88	88	88
Age of diagnosis (yrs ± SD)	36.3 (15.0) £	28.2 (12.4)	31.5 (13.8)	30.0 (16.2)	33(14.4)
Clinical features					
Clinical feature (%)					
Renal (ACR)	32#	63@	57†	40	60
Any renal	31$	74@@ @	56†	83	43
CNS (ACR)	9§§	37@@@	13	17	13
Any CNS	19	37*	23	33	14
Hematologic(ACR)	66	63	64	67	71
Any Pulmonary	27	53@@ §	34	50	14
Any Dermatologic	76	72	80	50	43
Serology					
ANA (% positive)	97.4	100	100	100	100
dsDNA (% positive)	72.3	63.2	72.9	83.3	71.4
ENAs tested-done (%)	63	77	54	63	75
SM	2.7$§§	41@@ @	22†	4	17
RNP	8$§§	65@@@	49‡	20	67
Ro	32	41	39	40	33
La	13	12	19	40	0
Sm + rnp	1.3	41.2	21.6	20	16.7
Ro + La	12.2	5.9	16.7	40	0
All ENAs	0	0	8.3	20	0

Socioeconomic Status					
Education					
recorded (%)	76	77	69	50	75
Education (years school)	13.2 (2.3) $	13.5 (2.5) **	10.1(2.4) ‡	14.8 (4.1)	11.2 (1.3)
Work status					
recorded (%)	77	77	75	63	88
Work status (%)					
Employed	43	53	28	40	71
Disabled	24	29	20	20	14
Retired	15	0	4	0	0
Unemployed	18	18	39	40	14
BC scale					
recorded (%)	43	36	46	25	63
BC scale	2.8£	3.1	3.3†	3	2.8

Table 6.2 Frequency of clinical features in Caucasians, Asian and NAI with SLE numbers represent % of patients with clinical feature ¶ includes arthralgias

† NAI vs Caucasians + Asian p<0.05; ††NAI vs Caucasian + Asians p<0.01; ‡ Caucasians vs NAI+ Asians p<0.05 £C vs N+A p<0.01; # Caucasian vs NAI + Asians p<0.001; * Asian vs NAI p<0.01; @ Asian vs Caucasian p<0.05; @@Asian vs Caucasian p<0.01; @@@Asian vs Caucasian p<0.001; § Asian vs Caucasian p<0.0001; $ Asians vs NAI + Caucasian p<0.01; §§ Asian vs NAI+ Caucasian p<0.05; & Fischer's exact

	Caucasian	Asian	NAI	whole cohort	p value
Diagnostic criteria					
Malar rash	47.4	57.9	56.6	49.5	NS
Discoid rash	18.0	21.1	20.4	18.6	NS
Photosensitivity	39.4	15.8*§§&	43.4	37.8	0.07
Oral/nasal ulcer	30.8	47.4	26.4	31.8	NS
Arthritis¶	82.8	94.7	91.8	85.6	NS
Pleuritis	26.5	42.1	30.4	28.2	NS
Pericarditis	8.7	21.1	14.0	10.2	NS
Cellular casts	9.3	36.8§$	23.2†	13.8	**0.0001**
Proteinuria	22.6£	52.6@@$	38.6†	28.2	**0.003**
Seizures	4.1‡	21.1@@§§&	7.0	6.0	**0.04**
Psychosis	5.2	26.3@@@$	8.8	7.4	**0.003**
Thrombocytopenia	19.1	10.5	20.7	18.3	NS
Hemolytic anemia	5.2£	21.1	10.9	7.8	**0.02**
Leukopenia	33.9	31.6	28.6	32.9	NS
Lymphopenia	51.1	47.4	50.9	50.9	NS
Additional clinical features					
Myositis	3.1‡	21.1@@&	5.2	16.7	**0.02**
Vasculitis	14.5‡	21.1	31.0††	17.7	**0.02**
Alopecia	25.4	47.4@	26.8	27.3	NS

Fever	14.7£	36.8@	29.1†	19.4	0.008
Reduced complement	65.2	73.7	77.7†	77.8	NS
Hematuria	14.6#	57.9*§	27.3	20.3	0.0001
Pyuria	3.7	5.3	9.1	4.9	NS
Organic brain syndrome	3.6	10.5	7.0	4.8	NS
Visual abnormality	4.1	5.3	1.8	3.7	NS
Cranial nerve abn	3.1	0	3.5	3.0	NS
Lupus headache	5.2	0	3.5	4.5	NS
CVA	8.8	5.3	10.5	8.9	NS

Table 6.3 Clinical outcome of ethnic groups with SLE
† NAI vs Caucasian + Asians p<0.05;††NAI vs Caucasian + Asians p<0.01;‡ NAI vs Caucasians + Asians p<0.0001;†† NAI vs Caucasian + Asians p<0.05;
# Caucasian vs NAI + Asians p<0.05, ## Caucasians vs NAI + Asians p<0.01

	Caucasian	**Asian**	**NAI**	**whole cohort**
SLICC score (at last clinic visit)	1.14#	1.61	1.87†	1.34
SLICC-renal	0.06##	0.05	0.24‡	0.10
SLICC- CNS	0.18	0.19	0.29	0.20
SLICC-pulmonary	0.05#	0.05	0.17††	0.07
Death (%)	5.8%#	9.1%	13.2% †	7.6%

Table 6.4 Proportion of patients with renal or CNS involvement testing positive for ENAs including all ethnicities. All values reported as number with +ve antibody/number with condition tested for antibody (%). *p< or = 0.05; + p<0.01; # p< or = 0.001; @ Fishers exact test

	Any Renal (N=116)	**renal (ACR)**	**any CNS**	**CNS (ACR)**
ENAs tested	86/116 (74%)	66/91 (73%)	41/61(67%)	20/34 (59%)
SM n/N (%)	15/86 (17%)+	14/66 (21%)+	10/41 (24%)#	10/20 (50%)#
RNP	24/84 (29%)	22/65 (34%)*	12/39 (31%)	10/19 (53%)#
Ro	30/84 (36%)	19/65 (29%)	9/38 (24%)	5/18 (28%)
La	12/84 (14%)	9/65 (14%)	4/39 (10%)	2/19 (11%)
SM + RNP	13/86 (15%)+	12/66 (18%)+	8/41 (20%)+	8/20 (40%)#
Ro + La	9/84 (11%)	6/65 (9%)	3/38 (8%)	1/18 (6%)
SM + RNP + Ro	5/85(6%)	4/65 (6%)	3/40 (8%)	3/19(16%)*@
SM + RNP + La	3/86 (4%)	3/66 (5%)	2/41 (5%)	2/20 (10%)
All ENAs +	2/85 (2%)	2/65 (3%)	1/40 (3%)	1/19 (5%)

Table 6.5 Proportion of patients with selective clinical features testing positive for ENAs including all ethnicities. All values are reported as the number of patients positive for the antibody per the number of patients with the clinical feature tested for the antibody (%). * p< or = 0.05; + p<0.01; # p<0.001; @Fishers exact test.

	SM	RNP	Ro	La
Diagnostic criteria				
Malar	15/106 (14)	26/100(26)	33/100 (33)	17/100(17)
Discoid rash	3/41 (7.3)	11/37 (30)	17/37 (46)	7/37 (19)
Photosensitivity	4/80 (5)*@	15/74 (20)	29/75 (39)	11/74 (15)
Oral/nasal ulcers	9/74 (12.1)	15/70 (21)	28/71 (39)	10/70 (14)
Arthritis	19/180 (11)	41/170 (24)	61/170 (36)	24/170 (14)
Pleuritis	8/61 (13)	16/57 (28)	24/58 (41)	10/57 (18)
Pericarditis	1/10 (10)	1/9(11)	4/9 (44)	1/9 (11)
Cellular casts	6/28 (21) *	10/28 (36)	8/27 (30)	6/28 (21)
Proteinuria	12/58 (21) +	19/57 (33)*	15/58 (26)	7/57 (12)
Seizures	5/10 (50) #	4/10 (40)	3/10 (30)	0/10 (0)
Psychosis	7/12 (58) #	7/11 (64) +@	4/10 (40)	2/11 (18)
Thrombocytopenia	4/37 (11)	6/35 (17)	12/35 (34)	3/35 (9)
Hemolytic anemia	1/18 (6)	5/16 (31)	3/17 (18)	0/16 (0)
Leukopenia	8/71 (11)	14/67 (21)	30/67 (45)	14/67 (21)
Lymphopenia	16/106 (15) *	29/98 (30)*	43/98 (44) *	21/98 (21)*
Additional clinical features				
Myositis	3/13 (23)21.4	4/12 (33)	2/12 (17) 15.4	0/12 (0)
Vasculitis	8/37 (21)*	12/35 (34)	15/34 (44)2.9	9/35 (26)
Alopecia	9/61 (15)	19/58 (33)*	22/57 (39)	7/58 (12)
Fever	9/44 (20)*	9/41 (22)	12/40 (30)	4/41 (10)

Reduced complement	19/140 (14)	35/132 (27)	54/132 (41)*	22/132 (17)
Hematuria	4/43 (9)	9/42 (21)	13/42 (31)	4/42 (10)
Pyuria	0/9 (0)	3/9 (33)	2/9 (22)	1/9 (11)
Organic brain syndrome	3/9 (33)	3/9 (33)	3/9 (33)	1/9 (11)
Visual abnormality	0/9 (0)	0/9/(0)	2/9 (22)	0/9 (0)
Cranial nerve abn	1/8 (13)	3/8 (38)	2/8 (25)	1/8 (13)
Lupus headache	1/12 (8)	2/12 (17)	5/12 (42)	4/12 (33)
CVA	2/18 (11)	4/18 (22)	4/18 (22)	3/18 (17)

Table 6.6 Sensitivity and specificity of SM and RNP for renal and neurologic lupus in the Manitoba cohort.
+LR: positive likelihood ration, -LR negative likelihood ratio

	Sensitivity	Specificity	+ LR	-LR
SM-renal	21 %	94%	0.22	0.83
SM-neurologic	50%	93%	0.53	0.53
RNP-renal	39%	82%	0.48	0.81
RNP-neurologic	19%	47%	0.40	1.71

Table 6.7a Predictors of SLICC at last visit
(Enter method)

	β (unstandardized)	CI β	p value
Ethnic	-0.04	-0.36 - 0.28	NS
Gender	-0.36	-1.09 - 0.38	NS
Education	*-0.12*	*-0.20 - -0.03*	*0.008*
Disease duration	***0.07***	***0.04 - 0.10***	***0.0001***
Anti-SM	-0.22	-1.07 - 0.62	NS
Anti-RNP	*0.81*	*0.19 - 1.43*	*0.006*

Table 6.7b Predictors of SLICC at last visit
(stepwise method controlling for all above variables)

	β (unstandardized)	CI β	p value
Education	*-0.20*	*-0.19- 0.04*	*0.004*
Disease duration	**0.07**	**0.04- 0.10**	**<0.0001**
Anti-RNP	*0.80*	*0.30- 1.30*	*0.002*

Model including only significant variables:

SLICC = 2.1 + 0.07 (disease duration in years) + 0.8(RNP) – 0.12 (years of education)

Table 6.8a Predictors of survival (disease duration) using Cox proportional hazard regression analysis (Enter method)

Model Chi-square 20.7($p<0.004$).
OR: Odds Ratio
CI OR: 95% confidence interval of Odds Ratio

	β (unstandardized)	SE β	OR	CI OR	p value
Education	0.25	0.18	1.30	0.91-1.82	NS
Gender	0.56	0.22	1.74	0.17-17.55	NS
Ethnicity					
NAI					***NS***
Asian	***1.73***	***1.27***	***5.62***	***0.46-68.05***	***NS***
Caucasian	***-1.60***	***2.33***	***0.20***	***0.002-19.67***	***NS***
Age at last visit	*0.09*	*0.04*	*1.09*	*1.01-1.12*	*0.01*
SLICC last visit	0.33	0.20	1.39	0.94-2.06	NS
Anti-SM	*-4.02*	*1.81*	*0.02*	*0.001-0.62*	*0.03*

Predictors of survival (disease duration) using Cox proportional hazard regression analysis (Forward conditional method)
Model Chi-square 11.3 ($p<0.001$).

	β (unstandardized)	SE β	OR	CI OR	p value
SM	***-2.5***	***-.94***	***0.08***	***0.01-0.52***	***0.008***

Table 6.8b Predictors of survival (age at last visit) using Cox proportional hazard regression analysis (Enter method)

Model Chi-square 23.3 (p=0.001)
OR: Odds Ratio
CI OR: 95% confidence interval of Odds Ratio

	β (unstandardized)	SE β	OR	CI OR	p value
Education	0.39	0.24	1.48	0.93-2.34	NS
Gender	1.45	1.39	4.28	0.28-65.96	NS
Ethnicity					
NAI					***NS***
Asian	***1.37***	***1.45***	***3.92***	***0.23-67.23***	***NS***
Caucasian	***-0.48***	***2.17***	***0.62***	***0.01-43.37***	***NS***
Disease duration	***0.05***	***0.10***	***0.96***	***0.79-1.15***	***NS***
SLICC last visit	*0.55*	*0.29*	*1.73*	*0.98-3.08*	*0.06*
Anti-SM	**-3.38**	**1.86**	**0.03**	**0.001-1.30**	**0.07**

Predictors of survival(age at last visit) using Cox proportional hazard regression analysis (Forward conditional method)
Model Chi-square 10.9 (p<0.001).

	β (unstandardized)	SE β	OR	CI OR	p value
SM	*-2.60*	*.98*	*0.08*	*0.01-0.51*	*0.008*

Table 6.8c Predictors of survival (disease duration) using Cox proportional hazard regression analysis (Enter method)

	Proportional hazard) CI PH		**p value**
Education	1.3	0.91-1.8	NS
Gender	1.7	1.7-19.6	NS
Age at last visit	1.1	1.0-1.2	0.01
Ethnicity			
NAI			***NS***
Asian	***5.6***	***0.46-68.0***	***NS***
Caucasian	***0.2***	***0.002-19.7***	***NS***
SLICC last visit	1.4	0.94-2.05	NS
Anti-SM	*0.02*	*0.001-0.62*	*0.3*

Predictors of survival using Cox proportional hazard regression analysis forward likelihood ratio (Forward conditional method)

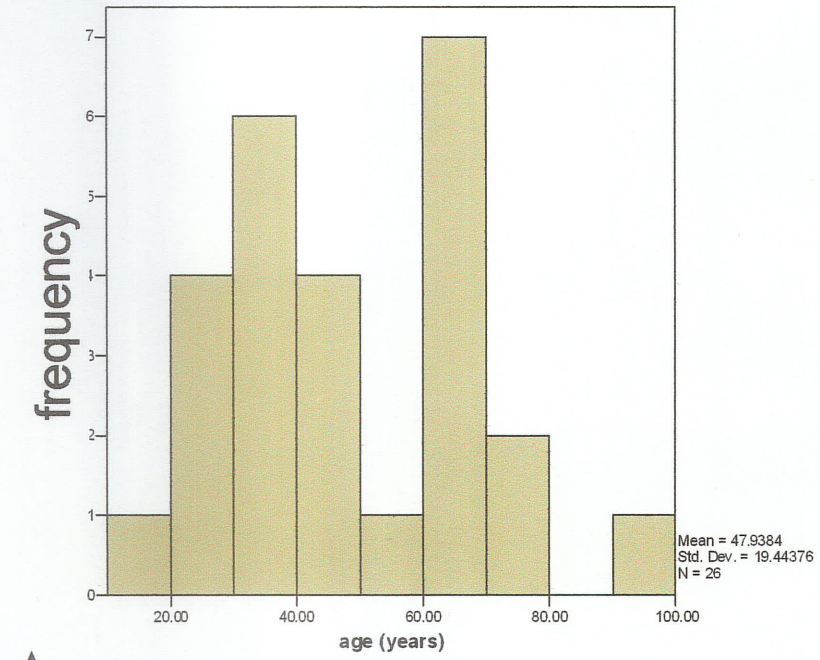
	β (unstandardized)	**SE β**	**p value**
SM	*0.08*	*0.01-0.52*	*0.008*

Proportional hazards equations:

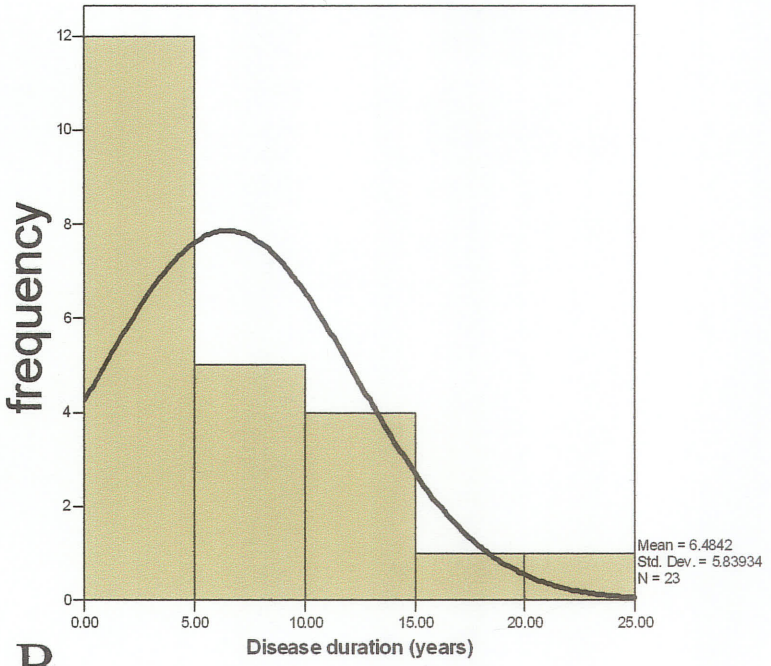
$\ln\alpha = 0.05(\text{age}) - 2.5\ (\text{SM})$

A patient age 40 and +ve for SM has 1.48 times the hazard of death than the average patient in the cohort.

$\ln\alpha = -2.5(\text{SM})$


frequency
7
6
5
4
3
2
1
0
20.00
40.00
60.00
80.00
100.00
age (years)
Mean = 47.9384
Std. Dev. = 19.44376
N = 26

A


frequency
12
10
8
6
4
2
0
0.00
5.00
10.00
15.00
20.00
25.00
Disease duration (years)
Mean = 6.4842
Std. Dev. = 5.83934
N = 23

B

Figure 6.1

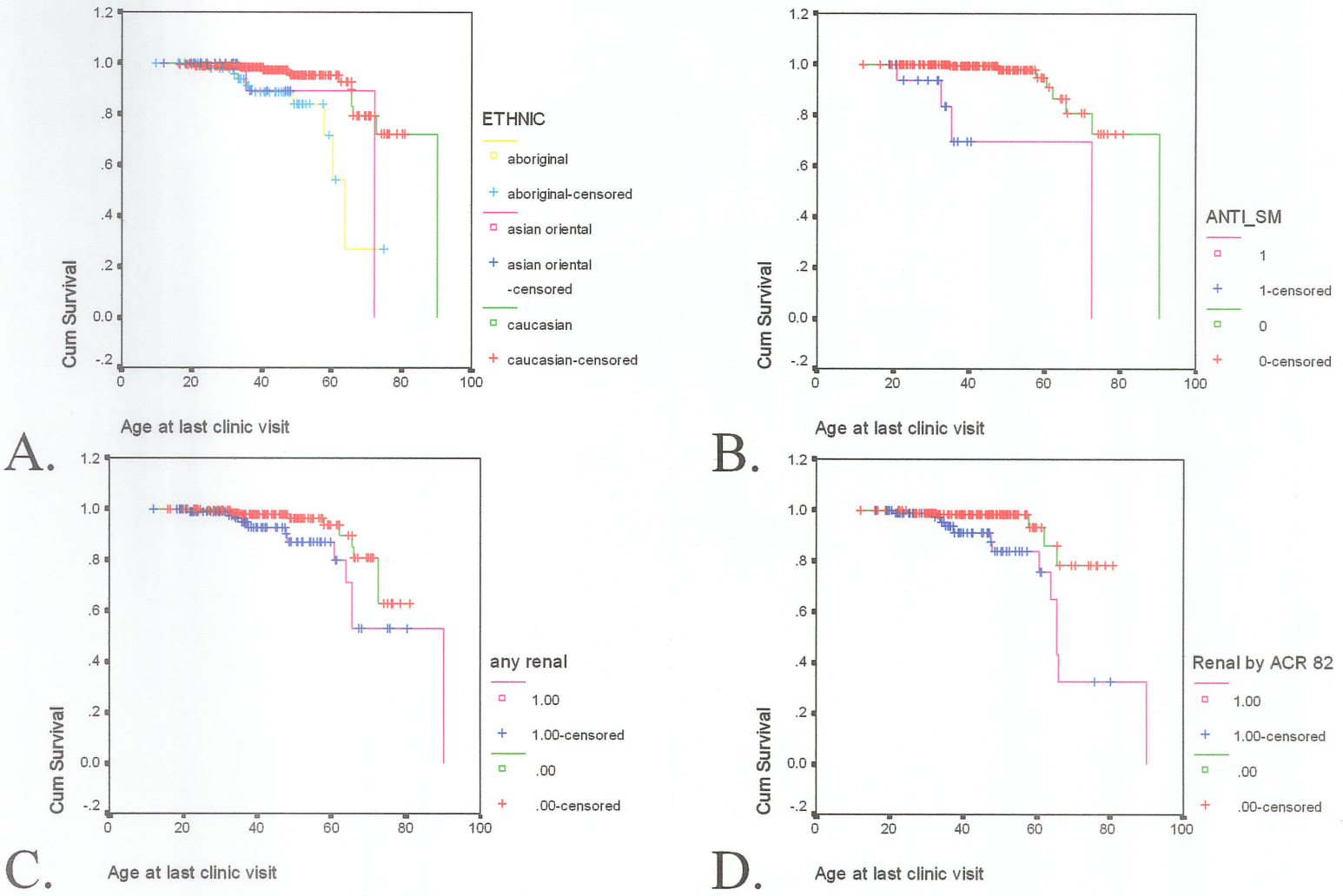
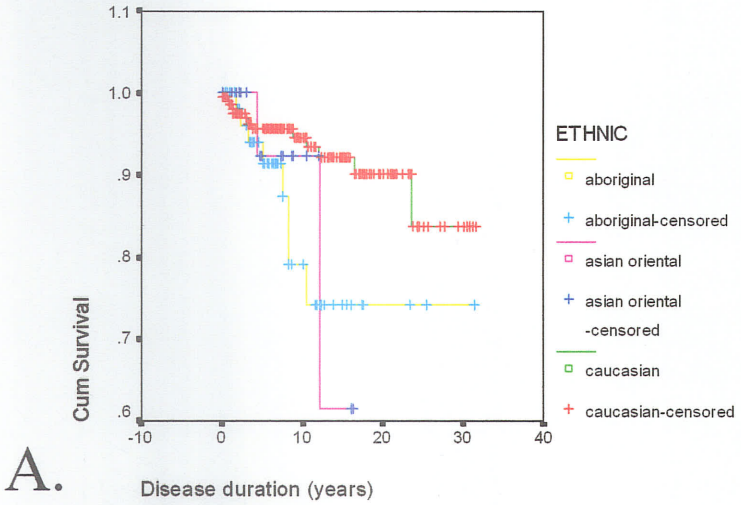
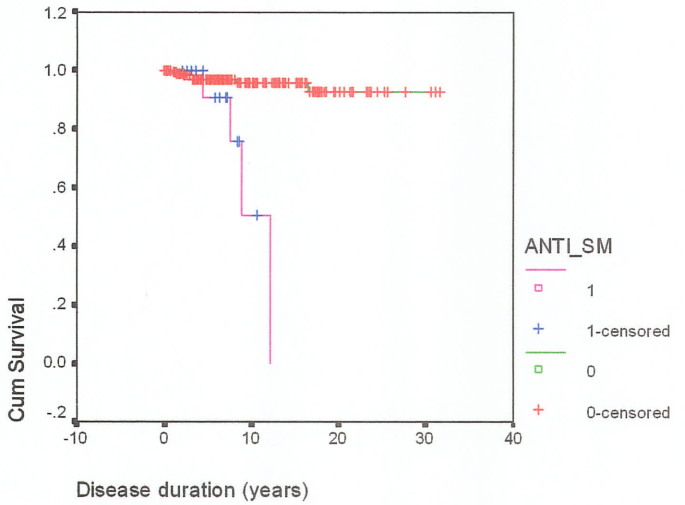

A.
Cum Survival
1.2
1.0
.8
.6
.4
.2
0.0
-.2
0
20
40
60
80
100
Age at last clinic visit
ETHNIC
aboriginal
aboriginal-censored
asian oriental
asian oriental -censored
caucasian
caucasian-censored
B.
Cum Survival
Age at last clinic visit
ANTI_SM
1
1-censored
0
0-censored
C.
Cum Survival
Age at last clinic visit
any renal
1.00
1.00-censored
.00
.00-censored
D.
Cum Survival
Age at last clinic visit
Renal by ACR 82
1.00
1.00-censored
.00
.00-censored

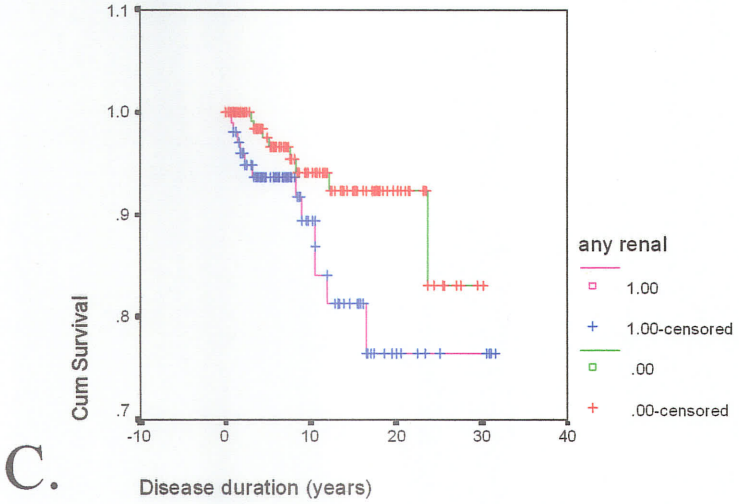
Figure 6.2



A.



B.



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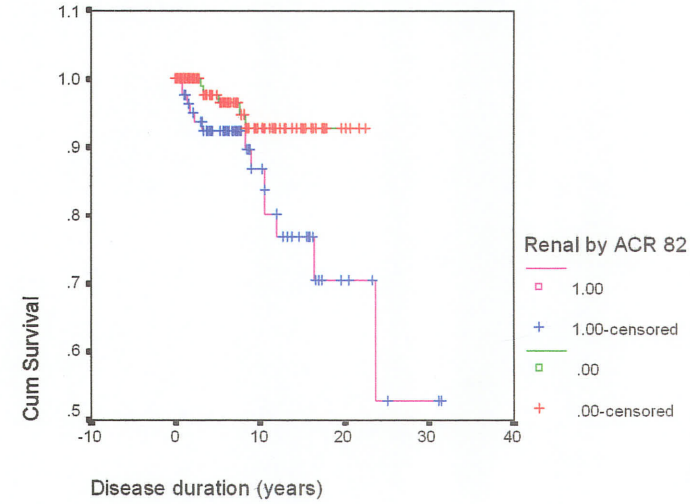

D.

Figure 6.3

Reference List

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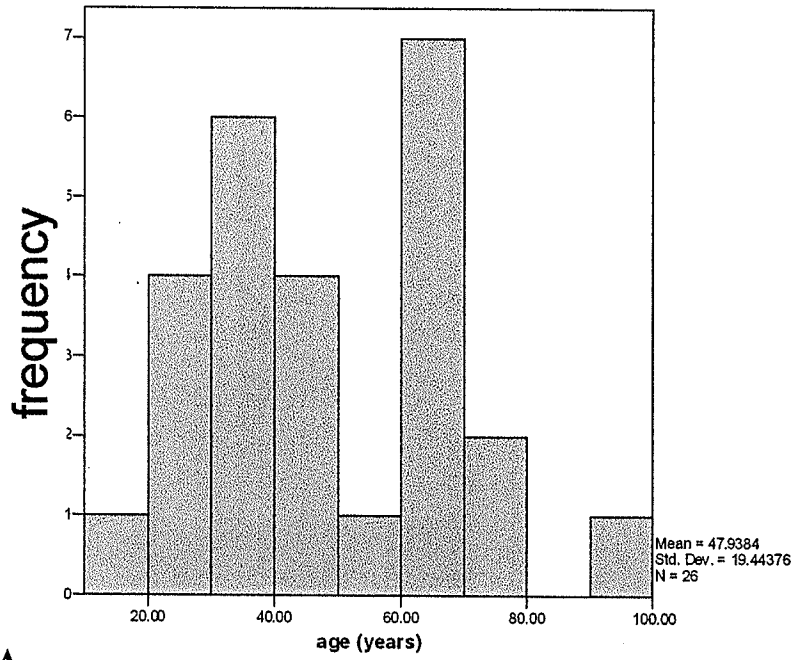
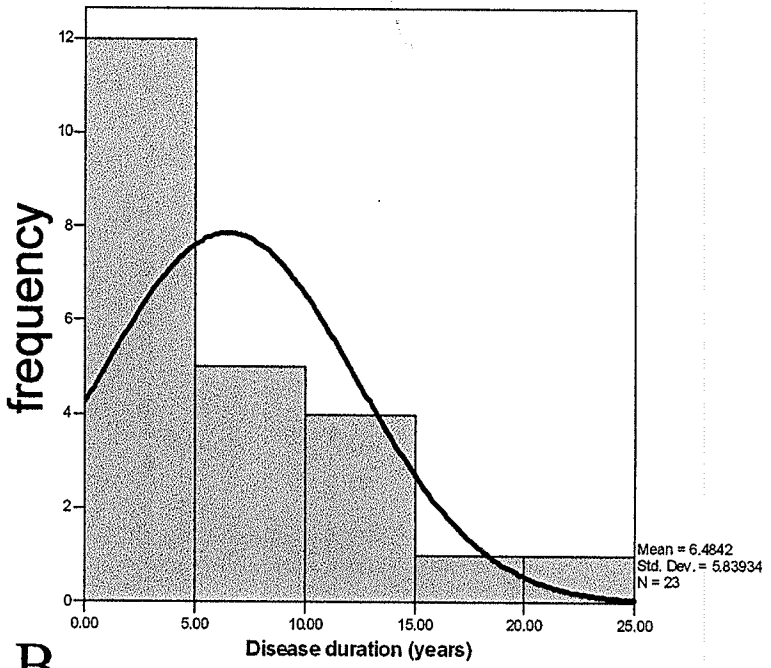
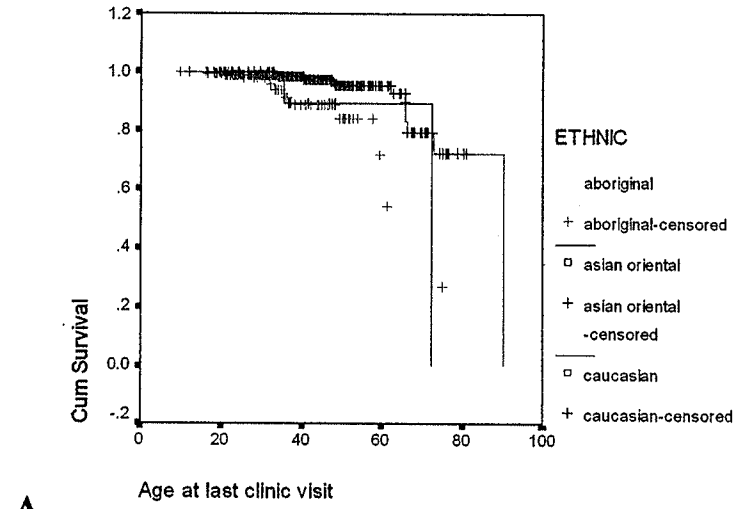

frequency
7
6
5
4
3
2
1
0
20.00
40.00
60.00
80.00
100.00
age (years)
Mean = 47.9384
Std. Dev. = 19.44376
N = 26

A


frequency
12
10
8
6
4
2
0
0.00
5.00
10.00
15.00
20.00
25.00
Disease duration (years)
Mean = 6.4842
Std. Dev. = 5.83934
N = 23

B

Figure 6.1



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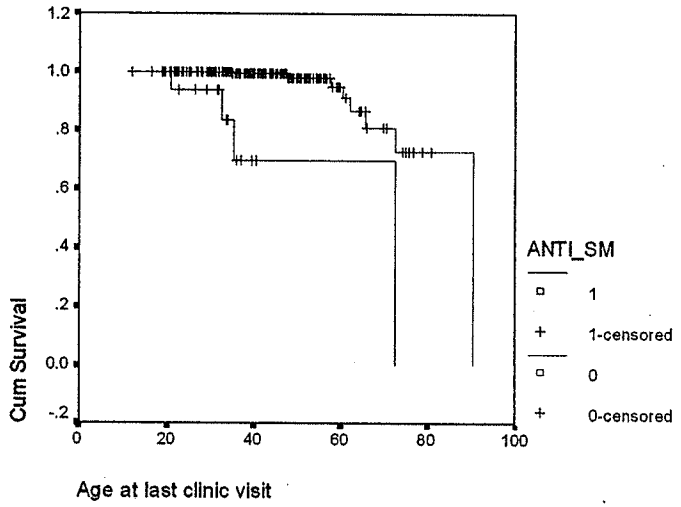

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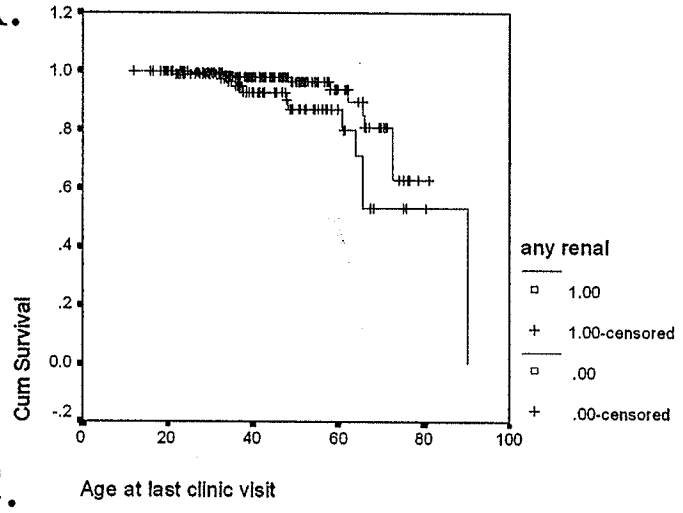
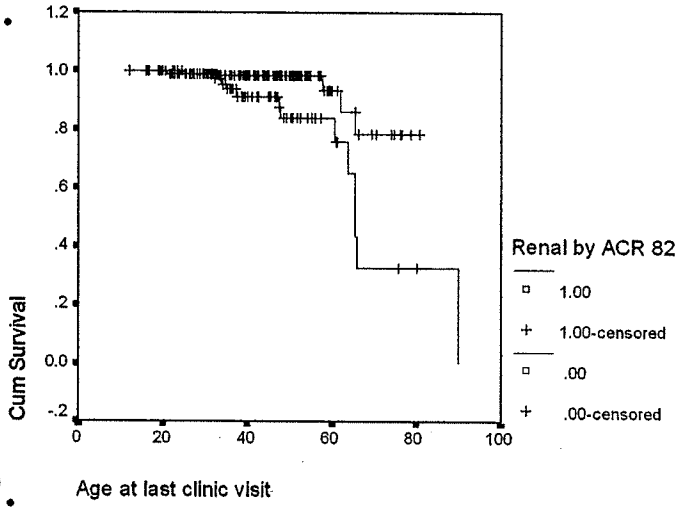
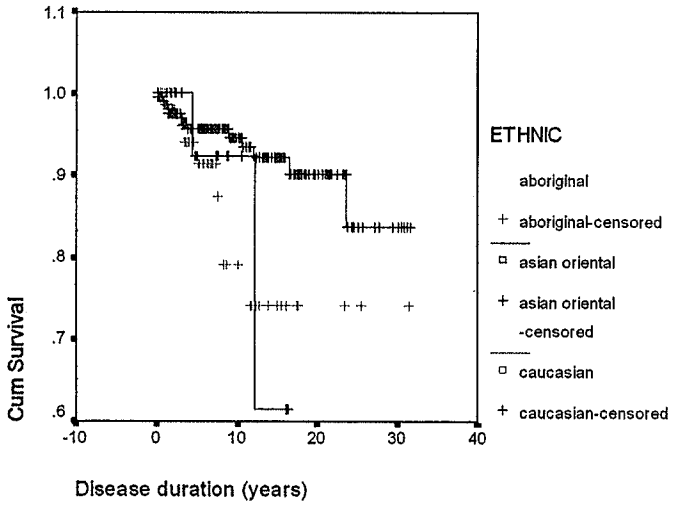


C.



D.

Figure 6.2



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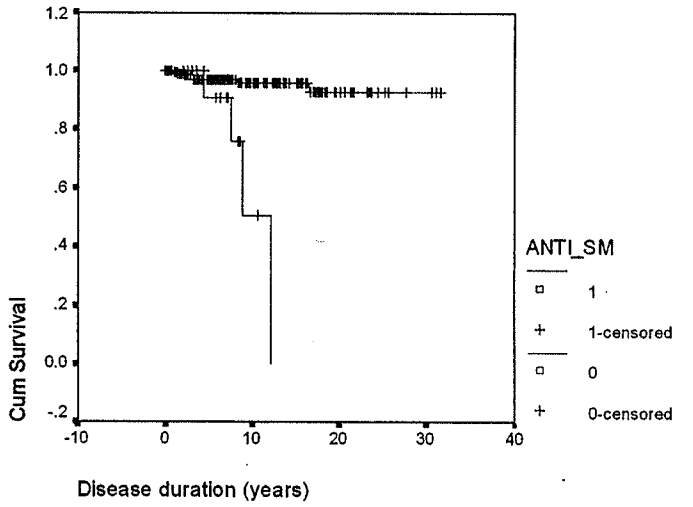

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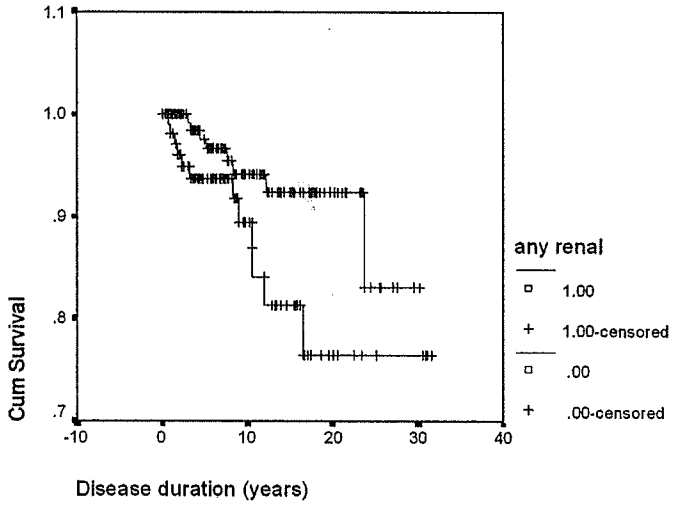

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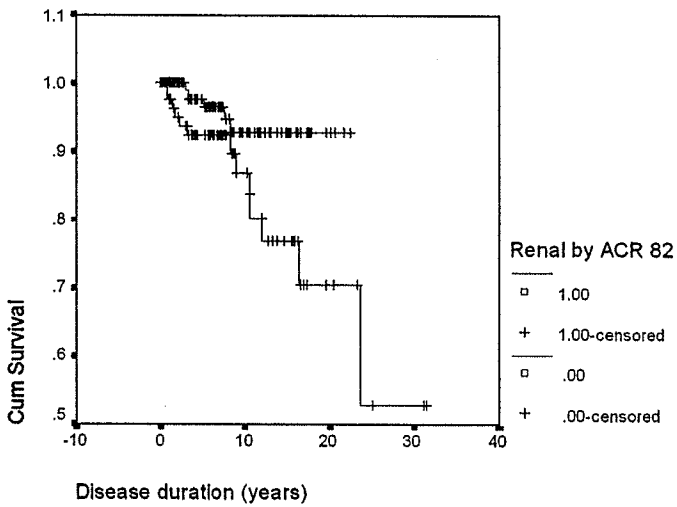

D.

Figure 6.3