Survival analysis of mortality and development of lupus nephritis in patients with systemic lupus erythematosus up to 40-years of follow-up

Weike Luo, Filipa Farinha, David A Isenberg, Anisur Rahman

Centre for Rheumatology Research, Division of Medicine, University College London, 5 University Street, London WC1E 6JF, UK

Corresponding Author and address for correspondence

Anisur Rahman

Centre for Rheumatology Research, Division of Medicine, UCL

Room 412, Rayne Building

5 University Street

London WC1E 6JF

Tel 00442034479035 Fax 00442034479278

e-mail anisur.rahman@ucl.ac.uk

ORCID ID http://orcid.org/0000-0003-2346-4484

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keac218/6567344 by University College London user on 19 April 2022

© The Author(s) 2022. Published by Oxford University Press on behalf of the British Society for Rheumatology.
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

Key messages

1) In this British cohort of patients with SLE, sex and ethnicity did not affect survival.

2) Patients diagnosed younger were more likely to develop lupus nephritis but less likely to die. Non-Caucasians were more likely to develop nephritis than Caucasians.

3) Patients diagnosed between 2006-11 had significantly improved survival compared to earlier cohorts.

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keac218/6567344 by University College London user on 19 April 2022

ABSTRACT

Objectives

Patients with systemic lupus erythematosus (SLE) have increased mortality compared to age and sex-matched controls. Lupus nephritis (LN) is a severe manifestation of SLE and an important cause of death. We carried out a retrospective survival analysis to investigate factors that could influence risk of mortality and LN in a large multi-ethnic cohort of patients with SLE.

Methods

By careful review of medical records, we identified 496 patients with SLE for whom we had complete information regarding period of observation and occurrence of death and nephritis. Patients were stratified into groups according to sex, ethnicity, age at start of follow-up and time-period of diagnosis. Kaplan-Meier analysis was used to investigate differences between the groups.

Results

Of 496 patients in the study, 91(18.3%) died,165(33.3%) developed LN and 33(6.7%) developed end-stage renal failure. There was no difference between men and women in either mortality or development of LN. Caucasian patients were significantly less likely to develop LN than other ethnic groups ($p<0.0001$) but not less likely to die. Patients diagnosed before the median age of 28 years were significantly more likely to develop LN ($p<0.0001$) but significantly less likely to die ($p=0.0039$) during the period of observation. There has been a significant

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keac218/6567344 by University College London user on 19 April 2022

improvement in survival between patients diagnosed between 1978 to 1989 and those diagnosed between 2006-11 (p=0.019).

Conclusion

In our cohort, non-Caucasian ethnicity and younger age at diagnosis are associated with risk of developing LN. There is evidence of improvement in survival of patients with SLE over time.

Key words

Systemic lupus erythematosus, mortality, lupus nephritis, ethnicity, survival analysis

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keac218/6567344 by University College London user on 19 April 2022

INTRODUCTION

Systemic Lupus Erythematosus (SLE) is an autoimmune rheumatic disease with a prevalence of 97 per 100,000 in the United Kingdom(1). Mortality from SLE has improved significantly over the last 50 years, but is still higher than for age and sex-matched people in the general population(2). It has been argued that the improvement in mortality was greatest prior to 2000(3) and has since levelled off and that it is not the same in countries with different levels of prosperity(3). Numerous studies in different countries have estimated the standardised mortality ratio (SMR) for SLE at between 2.5 and 5 with higher SMR in younger age groups(2, 4-15).

In calculating SMR, the mortality rate for patients with SLE is compared with that for the same age and sex groups in the area from which the SLE cohort was drawn. This approach has advantages. For example, Bernatsky *et al* pointed out that it allows for the fact that men in general have higher mortality than women and thus avoids over-estimating mortality risk in men with SLE compared to women with SLE(4). This method can be applied to very large groups such as the 9547 patients from multiple centers of the Systemic Lupus International Collaborative Clinics (SLICC) group studied by Bernatsky *et al(4)*.

The SMR method is not ideal for longitudinal analysis of survival in a group of patients that vary in terms of time of follow-up. Survival analysis using the Kaplan-Meier method is better from this point of view(16). However, when comparing

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keac218/6567344 by University College London user on 19 April 2022

survival curves in different subgroups of patients with SLE it is necessary to have sufficiently long follow-up, enough individuals and enough events to analyse in each subgroup. This can be a problem when looking at sex and ethnicity. For example, a Korean study only included female subjects because only one male patient with lupus had died(10). Many studies have been carried out in populations with little ethnic diversity, for example in Denmark(12), Sweden(9), Greece(13), Korea(10) and China(14, 15, 17).

It is important to define whether some groups of patients with SLE have higher mortality risk than others. Four characteristics of particular interest are sex, ethnicity, age at diagnosis and the time-period when the patients were diagnosed. The impact of these factors on mortality will be investigated in this paper using Kaplan-Meier survival analysis.

Though some groups have claimed higher mortality in men than women with SLE(11, 13, 17, 18), many others have found that this is not the case(4, 7, 8, 12, 15, 19, 20). A systematic review of 12 studies including 27,210 subjects also found no difference in SMR between men and women with SLE(2).

Papers from the USA have shown that African-American patients have higher mortality than white patients(18, 20-22) and this was also shown in the USA subgroup of the SLICC multi-centre study(4). This relationship, however, has not been demonstrated elsewhere and most SLE cohorts are not ethnically diverse

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keac218/6567344 by University College London user on 19 April 2022

enough to analyse the question. The United Kingdom has an ethnically diverse population but previous papers from Birmingham(23) and London(24) have not provided a clear answer to the question of association between mortality and ethnicity.

Patients diagnosed at a younger age have been reported by some groups to have more aggressive forms of disease and higher SMR(4-6, 8, 10, 25). On the other hand, not all reports agree(9, 12, 15) and because these younger patients are further from the end of a natural lifespan, survival analysis by the Kaplan-Meier method has shown that their survival over time is actually better on average than that of patients diagnosed later in life(17, 26).

Some groups have reported that SMR for patients with SLE improved considerably over time from 1970 to 2000(4, 27). However, in a meta-analysis of 171 studies, Tektonidou *et al* concluded that the improvement in mortality of patients with SLE seen up to 2000 has now slowed considerably(3). Most of those 171 papers, however, did not include data from later than 2005 so would not reflect improvements due to the introduction of biologic agents, for example(3). Singh and Yen reviewed national census data from the USA collected between 1968 and 2013 and concluded that mortality from SLE only started to fall in 1999 and fell steadily after that(20).

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keac218/6567344 by University College London user on 19 April 2022

Lupus nephritis (LN) is one of the most severe forms of SLE and a major cause of death in patients with this disease(28). A large study in the SLICC inception cohort showed that LN occurred in 700 of 1827 patients(29) and was associated with three-fold increase in risk of death. Risk factors for developing LN included male sex, non-white ethnicity and younger age(29). Other groups have reported similar findings(30, 31). We therefore expanded our analysis of the effects of ethnicity, sex and age of onset to include development of LN as well as mortality.

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keac218/6567344 by University College London user on 19 April 2022

PATIENTS AND METHODS

Patients

We reviewed medical records of patients treated at the Lupus Clinic at University College London Hospital (UCLH) since 1979. All met the American College of Rheumatology revised criteria for SLE(32) or previous criteria extant at the time of entry into the cohort. Causes of death in 725 patients treated at this unit have been described in a previous paper(24). That paper, however, did not include survival analysis because clear information about start and end of follow-up for each patient was not available.

In this paper we have included 496 patients for whom we have established accurately the duration of follow-up, occurrence and year of death, occurrence and year of diagnosis of lupus nephritis and date of censoring where appropriate. Any patient for whom all of these data-points could not be established (for example because they last had been seen many decades ago) was excluded from the analysis.

Whenever a patient fulfils classification criteria for SLE and is enrolled into this UCLH cohort a specific paper copy research folder is started, in which data including British Isles Lupus Activity Group (BILAG)-2004 activity score and medications are recorded at each clinic visit. In addition, a baseline serum sample is taken and stored. To

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keac218/6567344 by University College London user on 19 April 2022

establish accurate start date for follow-up one author (WL) reviewed all available research folders to find the earliest assessment and another (AR) reviewed the dates of the earliest sample in storage. Whichever was the earliest of these dates was taken as the start date for follow-up. Age at diagnosis was obtained by subtracting the birth year from the year of starting follow-up. We reviewed the data for all patients up to December 2019.

We categorized the patients into four groups by year of starting follow-up. These were Group 1 (1978-89, n=89), Group 2 (1990-99, n=155), Group 3 (2000-2005, n=112) and Group 4 (2006-2011, n=140). These groups were chosen so that no group covered too long a time-frame, so that the cut-points between groups were at the end of a calendar year (and for Groups 3 and 4) to coincide with introduction of new treatments. We began to use mycophenolate more extensively in 2000 and rituximab more widely in the mid-2000s.

To establish the end-date for follow-up, AR reviewed the medical records and research database to establish which patients remained under follow-up in 2019, which had died or been lost to follow-up and when these events had occurred.

Ethnicity and gender for each patient were entered by WL. A data quality check was carried out by AR double-checking a random 25% of the entries and there was agreement in 99.5% of datapoints. Ethnicity was categorized as Caucasian, Afro-

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keac218/6567344 by University College London user on 19 April 2022

Caribbean, South Asian (Indian, Pakistani, Bangladeshi, Sri Lankan), East Asian (Chinese, Japanese, Korean, Filipino) and other (including mixed ethnicity).

FF and DAI collected information for each patient with lupus nephritis. Ninety-five percent of the patients included had biopsy-proven LN(33). For the patients that either declined or had a contra-indication for renal biopsy, LN was assumed in the presence of two or more of the following – proteinuria>0.5 g/24 h; oedema requiring diuretic therapy; hypertension; creatinine clearance <60 ml/min; raised serum creatinine – in the absence of another explanation for these findings(34).

This is an observational retrospective study of medical records collected over a period of over 30 years. All data were derived from normal clinical management and no patients underwent extra questionnaires or research procedures. No individualized or identifiable data are presented in this study. Therefore, ethical approval and informed consent were not required. This is standard practice at our institution.

Statistical Analysis

Kaplan-Meier survival curves were compared using log-rank test and Hazard ratios (HRs) of mortality and incident LN were obtained through multivariate Cox regression analysis. All statistical tests were two-sided, conducted at a significance

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keac218/6567344 by University College London user on 19 April 2022

level of 0.05 and reported using p-values and/or 95% CIs. All statistical analyses were performed using a standard software package (Stata, version 16.1; StataCorp)

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keac218/6567344 by University College London user on 19 April 2022

RESULTS

The characteristics of patients enrolled in the study are shown in Table 1. Overall, there were 454 women and 42 men. Mean follow-up was 15.8 ± 8.75 years with a maximum of 40 years. Median age at start of follow-up was 28.0 (IQR 21 to 37 years).

There were 91 (18.3% of cohort) deaths and 165 (33.3%) patients developed LN. There were 35 (7.1%) patients who were in both these groups i.e. they developed LN and subsequently died – though only four patients died from LN itself. Of the 165 patients with LN, 33 eventually developed end stage renal disease (6.7% of cohort).

Cause of death

The main causes of death were cancer, cardiovascular/thrombosis, infection and renal disease. The causes of death in each group of patients are shown in Table 2.

Effect of sex

Death during the observation period occurred in 84/454 (18.5%) women and 7/42 (16.7%) men. Figure 1a shows that survival was not affected by gender. There were too few male deaths to reach conclusions about different causes of death between the sexes though no men died of either infection or renal disease.

LN occurred in 152/454 (33.5%) women and 13/42 (31.0%) men. Figure 1b shows that there was no difference between the groups in development of LN.

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keac218/6567344 by University College London user on 19 April 2022

Effect of ethnicity

Death occurred in 59/301(19.9%) Caucasian patients, 15/98 (15.3%) African/Caribbean patients, 12/55 (21.8%) South Asian patients and 2/24 (8.3%) East Asian patients. Figure 2a shows that the survival curves for the different ethnic groups are very similar with possible better survival in East Asians, though the curve only diverges from the other groups at a point where only two East Asians remained under follow-up making it hard to reach a firm conclusion. Statistical analysis showed no significant difference between the groups. Three of the four renal deaths occurred in Afro-Caribbean patients.

LN occurred in 77/307(25.1%) Caucasian patients, 44/98 (44.9%) African/Caribbean patients, 24/55 (43.6%) South Asian patients and 13/24 (54.2%) East Asian patients. Figure 2b shows that Caucasian patients had significantly lower risk of developing LN than any of the other ethnic groups.

By Cox proportional hazards analysis Afro-Caribbean patients had significantly increased risk of developing LN compared to Caucasians (HR 2.03, 95% CI 1.40-2.94, $p<0.0001$) and this was also true for South Asians (HR 1.85, 95% CI 1.17-2.93, $p=0.08$) and East Asians (HR 2.79, 95% CI 1.55-5.02, $p=0.01$).

Effect of age at start of follow-up

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keac218/6567344 by University College London user on 19 April 2022

Death occurred in 60/246 (24.3%) of patients diagnosed at above the median age of 28 years and 31/250 (12.4%) of patients diagnosed ≤ 28 years. Figure 3a shows a significant difference between the groups (p=0.0039). Apart from renal disease, all causes of death were over-represented in the older group with a particularly large difference for cardiovascular/thrombosis.

Whereas death was more likely to occur in the group diagnosed at an older age, the reverse was true for LN. LN developed in 107/250 (42.8%) of those diagnosed below the median age compared to 58/246 (23.6%) of those diagnosed above that age. Figure 3b shows that this difference is significant (p<0.0001).

Effect of time of diagnosis

After stratification of the patients into four groups according to the date of starting follow-up, 39/89 (38.2%) of Group 1, 34/155 (21.9%) of Group 2, 14/112 (12.5%) of Group 3 and 4/140 (2.9%) of Group 4 had died during the period of observation. Figure 4a shows an improvement in survival going from Group 1 to Group 4 that was statistically significant (p=0.019).

LN occurred in 36/89 (40.4%) of Group 1, 38/155 (24.5%) of Group 2, 55/112 (49.1%) of Group 3 and 36/140 (25.7%) of Group 4. Figure 4b shows a statistically significant increase in diagnosis of LN in Group 3 compared to the other groups (p<0.05).

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keac218/6567344 by University College London user on 19 April 2022

Using Cox proportional hazards analysis, there was a significantly lower risk of mortality for Group 4 compared to group 1 – hazard ratio (HR) = 0.22, 95% CI 0.07-0.63, p=0.005. Significant differences were not seen for the other groups; Group 2 vs Group 1 HR 0.69, 95% CI 0.42-1.11, Group 3 vs Group 1 HR 0.63, 95% CI 0.43-1.18.

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keac218/6567344 by University College London user on 19 April 2022

DISCUSSION

This is the largest survival analysis study ever undertaken in a British SLE cohort. By retrospective analysis of data from 496 patients, with representation of four ethnic groups, we have obtained new insights into effects of sex, ethnicity, age at onset and time-period of diagnosis.

Our results concur with studies from different units showing no difference in mortality between men and women with SLE(4, 7, 8, 12, 15, 19, 20). A limitation is that there may have been too few men in our study to detect increase in mortality or development of LN. Studies showing higher mortality in men with SLE(11, 13, 17, 18) have been from single centers (like our study), so the effect may be center-dependent. Wu *et al* considered the possibility that the apparent increased male mortality could be due to worse renal function and older age at onset in men in their cohort(17). In a large study (1979 patients,157 men), Tan *et al* reported that 11.5% of men but 6.2% of women died(18). However, both Singh and Yen in the USA and Bultink *et al* in Britain, reviewing census data of SLE deaths from national databases concluded that women had higher mortality than men(19, 20) (though in the latter case this was not statistically significant). Unlike other studies(12, 18, 29), we did not find increased LN in men, but the number of men with LN in those studies was much higher than in ours. Feldman *et al* focused on patients with incident LN identified from the Medicaid Analytic Extract from 29 American states. In this large study, 2467 women and 283 men were identified and five-year cumulative mortality was 9.4% in man and 9.8% in women with no difference in mortality or end-stage renal disease between the sexes. (35)

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keac218/6567344 by University College London user on 19 April 2022

We found that non-Caucasian patients were not more likely to die than Caucasians. In fact, the only data showing that black patients with SLE, in particular, have higher risk of mortality come from the USA(18, 21, 22). The population studied by Lim *et al* in Georgia was notable for a very high proportion of black patients (76%) and a high death rate (401/1353)(18, 21) especially amongst black patients. In Baltimore, Tan *et al* studied 1979 patients (131 deaths – 77 were in black people and 54 in Caucasians) and concluded that black patients of both sexes had an increased risk of death(18). In the USA, however, associations between ethnicity, poverty and access to healthcare may mean that relationships between ethnicity and health outcomes may not be representative of other countries(36). Guo *et al* pointed out that all-cause mortality is also significantly higher for black than white American women(22). Singh and Yen found that relationships between ethnicity and mortality in SLE depended on geographical location within the USA and, in particular, that higher mortality occurred in areas with higher poverty rates (20). Only one study outside the USA has looked at the effect of ethnicity on mortality in patients with SLE. Hendler *et al* studied 600 patients in Brazil, of whom 54 died(26). However, ethnicity was only described in terms of European descent and was not associated with mortality in multivariate analysis. In the UK, though there are socio-economic differences between ethnic groups, healthcare is free at the point of delivery. Based on our findings, we therefore suggest that socio-economic factors and access to healthcare are likely to have been more important than genetic factors in the reports of higher mortality in black patients with SLE in the USA. We recognize, however, that the genetic background of African-Americans is different from that of Afro-Caribbean patients in the UK.

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keac218/6567344 by University College London user on 19 April 2022

We confirmed findings from other groups that LN is more common in non-Caucasian patients(18, 29). The reasons for this difference are not fully understood. The fact that it was not reflected in increased deaths in non-Caucasians may be due to improved treatment of LN. Only four patients within our cohort died from renal lupus – though 35 of 91 patients who died from any cause had a previous history of LN(24).

Patients diagnosed with SLE earlier in life, particularly those with juvenile onset(5, 37), tend to have more active disease and higher prevalence of major organ involvement such as LN. The situation with regard to mortality depends on the method of analysis used. Papers that cite SMR almost invariably show higher SMR in younger age groups(4-7, 10, 12, 25), where the death rate amongst the non-lupus population is very low. Papers that do not use SMR and/or describe cumulative deaths by means of survival analysis, however, show that patients diagnosed later in life are more likely to die within a given time-period(17, 26). Our results support these previous findings. Patients diagnosed with SLE below the median age were more likely to develop LN, but less likely to die during the period of observation. It may be, however, that our follow-up is still not prolonged enough to reach firm conclusions about this point. Damage due to early aggressive treatment of SLE may take many decades to impact on mortality, for example.

The concept that mortality from SLE has improved over time has been supported by numerous studies in which authors subdivided cohorts of patients with SLE according to time-period of diagnosis and reported lower SMRs in the patients

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keac218/6567344 by University College London user on 19 April 2022

diagnosed more recently. Bernatsky *et al*, studying 9547 patients, reported SMR of 4.9 in those diagnosed between 1970-79 but 2.0 in those diagnosed between 1990 and 2001(4). In 442 patients from Hong Kong, Mok *et al* reported a fall in SMR from 7.88 to 2.17 between 2000 and 2006(6). In 1241 Canadian patients, Urowitz *et al* showed that SMR was 12.6 for those diagnosed between 1970-78 and 3.46 for those diagnosed between 1997 and 2005(11). Conversely, Ingvarsson *et al* found no improvement in mortality over time in 175 Swedish patients followed from 1981 to 2014(9) and a review of 125 studies of adult SLE suggested that improvement might have plateaued after the mid-1990s(3).

Our study has the advantages of follow-up till 2019 and the generation of survival curves for the different time-groups. Figure 4b clearly shows an improvement over time, which is statistically significant comparing Group 4 to Group 1. Reasons for this improvement, as discussed by other authors, could include diagnosis of milder cases and improvements in therapy(3). The latter explanation would suggest that deaths from lupus itself (rather than infection, cancer or cardiovascular disease) should be less frequent in later cohorts, which has been shown by some authors(4, 7). In our study, however, very few deaths were due directly to SLE so we can make no such conclusion.

We were surprised by the finding that cases of LN were significantly higher in Group 3 than the other groups. On further examination of the data, it seems likely that this is a coincidental finding due to the fact that significantly more African/Caribbean patients entered the cohort during the period 2000-2005 than at other times. Thus,

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keac218/6567344 by University College London user on 19 April 2022

the proportions of African/Caribbean patients were 14/89 (15.7%) in Group 1, 21/155 (13.5%) in Group 2, 26/112 (32.1%) in Group 3 and 27/140 (19.3%) in Group 4.

Limitations of the study include the fact that it is from a single centre and that, since the data were gathered over a period of many years, the results may have been affected by changes in referral practice, physicians and standards of care. Since this is a rheumatology department, patients with LN and advanced kidney failure may not be referred. This is the group with the highest mortality. Very few of our patients died of LN.

In conclusion, this very large, long-duration survival analysis study in an ethnically diverse British cohort of patients with SLE has shown that mortality does seem to be improving in patients diagnosed more recently. Greater mortality in African American patients with SLE may be a specific USA finding related to socio-economic factors.

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keac218/6567344 by University College London user on 19 April 2022

ACKNOWLEDGEMENTS

FF was supported by Fundação para a Ciência e a Tecnologia, IP Grant DFA/BD/7131/2020 and LUPUS UK Grant 1543411.

AUTHORSHIP CONTRIBUTIONS

WL, FF, DAI and AR all collected data. WL, FF and AR carried out statistical analysis. AR wrote the final manuscript. WL, FF, DAI and AR all contributed to critical analysis of the manuscript and approved the final version.

COMPETING INTERESTS STATEMENT

The authors have declared no conflicts of interest.

FUNDING STATEMENT

This work was carried out at a center supported by the National Institute for Health Research University College London Hospitals Biomedical Research Centre.

DATA AVAILABILITY STATEMENT

Data are available on request to the authors

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keac218/6567344 by University College London user on 19 April 2022

REFERENCES

1. Rees F, Doherty M, Grainge M, Davenport G, Lanyon P, Zhang W. The incidence and prevalence of systemic lupus erythematosus in the UK, 1999-2012. Ann Rheum Dis. 2016;75(1):136-41.

2. Yurkovich M, Vostretsova K, Chen W, Avina-Zubieta JA. Overall and cause-specific mortality in patients with systemic lupus erythematosus: a meta-analysis of observational studies. Arthritis care & research. 2014;66(4):608-16.

3. Tektonidou MG, Lewandowski LB, Hu J, Dasgupta A, Ward MM. Survival in adults and children with systemic lupus erythematosus: a systematic review and Bayesian meta-analysis of studies from 1950 to 2016. Ann Rheum Dis. 2017;76(12):2009-16.

4. Bernatsky S, Boivin JF, Joseph L, Manzi S, Ginzler E, Gladman DD, et al. Mortality in systemic lupus erythematosus. Arthritis Rheum. 2006;54(8):2550-7.

5. Hersh AO, Trupin L, Yazdany J, Panopalis P, Julian L, Katz P, et al. Childhood-onset disease as a predictor of mortality in an adult cohort of patients with systemic lupus erythematosus. Arthritis care & research. 2010;62(8):1152-9.

6. Mok CC, To CH, Ho LY, Yu KL. Incidence and mortality of systemic lupus erythematosus in a southern Chinese population, 2000-2006. J Rheumatol. 2008;35(10):1978-82.

7. Bjornadal L, Yin L, Granath F, Klareskog L, Ekbom A. Cardiovascular disease a hazard despite improved prognosis in patients with systemic lupus erythematosus: results from a Swedish population based study 1964-95. J Rheumatol. 2004;31(4):713-9.

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keac218/6567344 by University College London user on 19 April 2022

8. Bernatsky S, Clarke A, Gladman DD, Urowitz M, Fortin PR, Barr SG, et al. Mortality related to cerebrovascular disease in systemic lupus erythematosus. Lupus. 2006;15(12):835-9.

9. Ingvarsson RF, Landgren AJ, Bengtsson AA, Jonsen A. Good survival rates in systemic lupus erythematosus in southern Sweden, while the mortality rate remains increased compared with the population. Lupus. 2019;28(12):1488-94.

10. Chun BC, Bae SC. Mortality and cancer incidence in Korean patients with systemic lupus erythematosus: results from the Hanyang lupus cohort in Seoul, Korea. Lupus. 2005;14(8):635-8.

11. Urowitz MB, Gladman DD, Tom BD, Ibanez D, Farewell VT. Changing patterns in mortality and disease outcomes for patients with systemic lupus erythematosus. J Rheumatol. 2008;35(11):2152-8.

12. Jacobsen S, Petersen J, Ullman S, Junker P, Voss A, Rasmussen JM, et al. A multicentre study of 513 Danish patients with systemic lupus erythematosus. II. Disease mortality and clinical factors of prognostic value. Clin Rheumatol. 1998;17(6):478-84.

13. Alamanos Y, Voulgari PV, Papassava M, Tsamandouraki K, Drosos AA. Survival and mortality rates of systemic lupus erythematosus patients in northwest Greece. Study of a 21-year incidence cohort. Rheumatology (Oxford). 2003;42(9):1122-3.

14. Mok CC, Kwok CL, Ho LY, Chan PT, Yip SF. Life expectancy, standardized mortality ratios, and causes of death in six rheumatic diseases in Hong Kong, China. Arthritis Rheum. 2011;63(5):1182-9.

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keac218/6567344 by University College London user on 19 April 2022

15. Mu L, Hao Y, Fan Y, Huang H, Yang X, Xie A, et al. Mortality and prognostic factors in Chinese patients with systemic lupus erythematosus. Lupus. 2018;27(10):1742-52.

16. Altman DG. Practical Statistics for Medical Research. London: Chapman & Hall; 1991.

17. Wu G, Jia X, Gao D, Zhao Z. Survival rates and risk factors for mortality in systemic lupus erythematosus patients in a Chinese center. Clin Rheumatol. 2014;33(7):947-53.

18. Tan TC, Fang H, Magder LS, Petri MA. Differences between male and female systemic lupus erythematosus in a multiethnic population. J Rheumatol. 2012;39(4):759-69.

19. Bultink IEM, de Vries F, van Vollenhoven RF, Lalmohamed A. Mortality, causes of death and influence of medication use in patients with systemic lupus erythematosus vs matched controls. Rheumatology (Oxford). 2021;60(1):207-16.

20. Singh RR, Yen EY. SLE mortality remains disproportionately high, despite improvements over the last decade. Lupus. 2018;27(10):1577-81.

21. Lim SS, Helmick CG, Bao G, Hootman J, Bayakly R, Gordon C, et al. Racial Disparities in Mortality Associated with Systemic Lupus Erythematosus - Fulton and DeKalb Counties, Georgia, 2002-2016. MMWR Morb Mortal Wkly Rep. 2019;68(18):419-22.

22. Guo Q, Liang M, Duan J, Zhang L, Kawachi I, Lu TH. Age differences in secular trends in black-white disparities in mortality from systemic lupus erythematosus among women in the United States from 1988 to 2017. Lupus. 2021;30(5):715-24.

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keac218/6567344 by University College London user on 19 April 2022

23. Yee CS, Su L, Toescu V, Hickman R, Situnayake D, Bowman S, et al. Birmingham SLE cohort: outcomes of a large inception cohort followed for up to 21 years. Rheumatology (Oxford). 2015;54(5):836-43.

24. Lorenzo-Vizcaya A, Isenberg D. Analysis of trends and causes of death in SLE patients over a 40-years period in a cohort of patients in the United Kingdom. Lupus. 2021;30(5):702-6.

25. To CH, Mok CC, Tang SS, Ying SK, Wong RW, Lau CS. Prognostically distinct clinical patterns of systemic lupus erythematosus identified by cluster analysis. Lupus. 2009;18(14):1267-75.

26. Hendler JV, de Souza L, de Freitas Zernow DC, Guimaraes J, Bertotto T, Saldanha CF, et al. Survival analysis of patients with systemic lupus erythematosus in a tertiary hospital in southern Brazil. Clin Rheumatol. 2017;36(9):2005-10.

27. Urowitz MB, Gladman DD, Abu-Shakra M, Farewell VT. Mortality studies in systemic lupus erythematosus. Results from a single center. III. Improved survival over 24 years. J Rheumatol. 1997;24(6):1061-5.

28. Yap DY, Tang CS, Ma MK, Lam MF, Chan TM. Survival analysis and causes of mortality in patients with lupus nephritis. Nephrol Dial Transplant. 2012;27(8):3248-54.

29. Hanly JG, O'Keeffe AG, Su L, Urowitz MB, Romero-Diaz J, Gordon C, et al. The frequency and outcome of lupus nephritis: results from an international inception cohort study. Rheumatology (Oxford). 2016;55(2):252-62.

30. Lim SS, Bayakly AR, Helmick CG, Gordon C, Easley KA, Drenkard C. The incidence and prevalence of systemic lupus erythematosus, 2002-2004: The Georgia Lupus Registry. Arthritis & rheumatology. 2014;66(2):357-68.

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keac218/6567344 by University College London user on 19 April 2022

31. Somers EC, Marder W, Cagnoli P, Lewis EE, DeGuire P, Gordon C, et al. Population-based incidence and prevalence of systemic lupus erythematosus: the Michigan Lupus Epidemiology and Surveillance program. Arthritis & rheumatology. 2014;66(2):369-78.

32. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1997;40(9):1725.

33. Weening JJ, D'Agati VD, Schwartz MM, Seshan SV, Alpers CE, Appel GB, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. J Am Soc Nephrol. 2004;15(2):241-50.

34. Gisca E, Duarte L, Farinha F, Isenberg DA. Assessing outcomes in a lupus nephritis cohort over a 40-year period. Rheumatology (Oxford). 2021;60(4):1814-22.

35. Feldman CH, Broder A, Guan H, Yazdany J, Costenbader KH. Sex Differences in Health Care Utilization, End-Stage Renal Disease, and Mortality Among Medicaid Beneficiaries With Incident Lupus Nephritis. Arthritis & rheumatology. 2018;70(3):417-26.

36. Duran S, Apte M, Alarcon GS, Group LS. Poverty, not ethnicity, accounts for the differential mortality rates among lupus patients of various ethnic groups. J Natl Med Assoc. 2007;99(10):1196-8.

37. Ambrose N, Morgan TA, Galloway J, Ionnoau Y, Beresford MW, Isenberg DA, et al. Differences in disease phenotype and severity in SLE across age groups. Lupus. 2016;25(14):1542-50.

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keac218/6567344 by University College London user on 19 April 2022

Figure Legends

Figure 1 -Effect of sex on mortality and lupus nephritis

Comparison of a) Mortality and b) Incidence of lupus nephritis between male and female patients.

Figure 2 – Effect of ethnicity on mortality and lupus nephritis

Comparison of a) Mortality and b) Incidence of lupus nephritis between patients in different ethnic groups; Caucasian, Afro-Caribbean, South Asian, East Asian.

Figure 3 -Effect of age at onset of SLE on mortality and lupus nephritis

Comparison of a) Mortality and b) Incidence of lupus nephritis between patients diagnosed with SLE above and below the median age (28 years old).

Figure 4 – Effect of time period of diagnosis on mortality and lupus nephritis

Comparison of a) Mortality and b) Incidence of lupus nephritis between patients diagnosed with SLE during the following time periods; Group 1 (1978-89), Group 2 (1990-99), Group 3 (2000-5), Group 4 (2006-11)

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keac218/6567344 by University College London user on 19 April 2022

TABLE 1. DEMOGRAPHIC AND CLINICAL CHARACTERISTIC OF PATIENTS ENROLLED

Variables	Number of Patients	Number of Deaths	Number of Patients with LN
n Total	496	91	165
Gender			
Female	454 (91.5%)	84 (92.3%)	152 (92.1%)
Male	42 (8.47%)	7 (7.69%)	13 (7.88%)
Age at onset			
Above median (>28 years)	246 (50.4%)	60 (65.9%)	58 (35.2%)
Below median (≤28 years)	250 (49.6%)	31 (34.1%)	107 (64.9%)
Ethnicity			
Caucasian	307 (61.9%)	59 (64.8%)	77 (46.7%)
South Asian	55 (11.1%)	12 (13.2%)	24 (14.6%)
African Caribbean	98 (19.8%)	15 (16.5%)	44 (26.7%)
East Asian	24 (4.8%)	2 (2.2%)	13 (7.88%)
Mixed Race	12 (2.42%)	3 (3.3%)	7 (4.24%)

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keac218/6567344 by University College London user on 19 April 2022

Diagnosis Time Group			
1978 – 1989	89 (17.9%)	39 (42.9%)	36 (21.8%)
1990 – 1999	155 (31.3%)	33 (36.4%)	38 (23.0%)
2000 – 2005	112 (22.6%)	15 (16.5%)	55 (33.0%)
2006 – 2011	140 (28.2%)	4 (4.4%)	36 (21.8%)

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keac218/6567344 by University College London user on 19 April 2022

TABLE 2 – CAUSES OF DEATH

	Infection	*Cardiovascular/thrombosis*	*Cancer*	*Renal*	*Other*	*Total*
Total	25	18	25	4	19	91
By sex						
Male	0	3 (17%)	3 (12%)	0	1 (5%)	7 (8%)
Female	25 (100%)	15 (83%)	22 (88%)	4 (100%)	18 (95%)	84 (92%)
By ethnicity						
Caucasian	13 (52%)	14 (78%)	22 (88%)	1 (25%)	9 (47%)	59 (65%)
Afro-Caribbean	5 (20%)	1 (5.5%)	1 (4%)	3 (75%)	5 (26%)	15 (16%)
South Asian	4 (16%)	2 (11%)	2 (8%)	0	4 (21%)	12 (13%)
East Asian	0	1 (5.5%)	0	0	1 (5%)	2 (2%)
Mixed	3 (12%)	0	0	0	0	3 (3%)
By age of onset						
Above median	16 (64%)	15 (83%)	16 (64%)	2 (50%)	12 (63%)	61 (67%)
Below median	9 (36%)	3 (17%)	9 (36%)	2 (50%)	7 (37%)	30 (33%)
By Time of Diagnosis						

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keac218/6567344 by University College London user on 19 April 2022

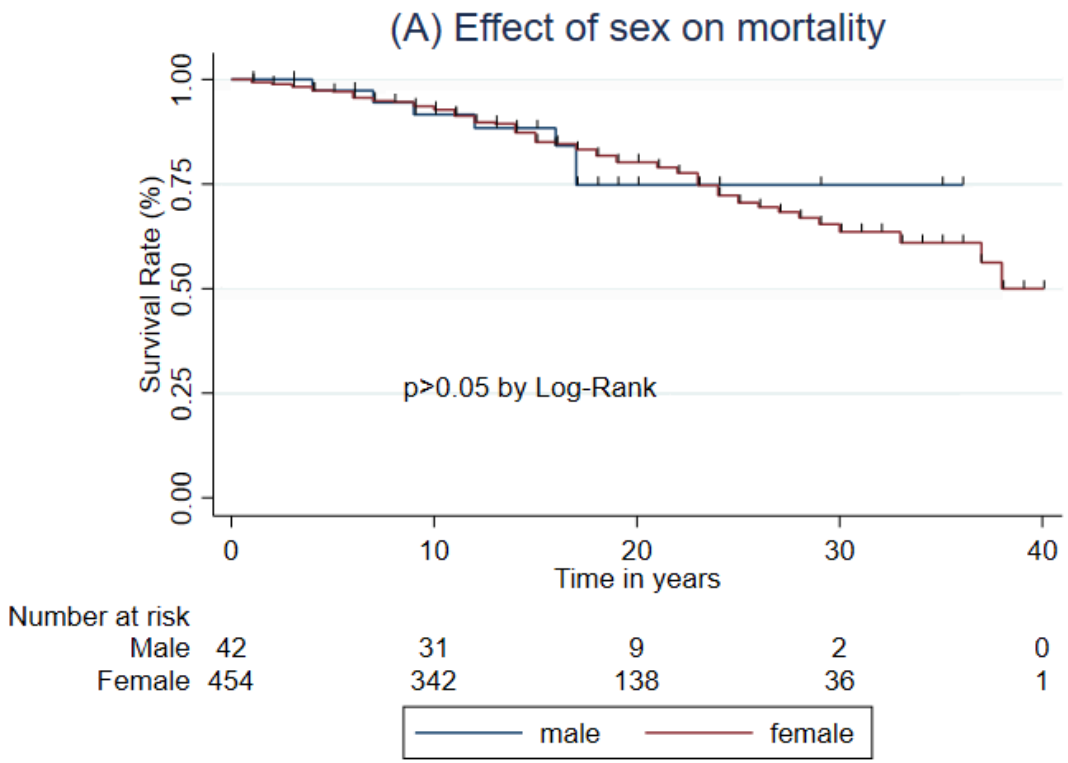
Group 1	10 (40%)	7 (39%)	10 (40%)	3 (75%)	9 (47%)	39 (43%)
Group 2	8 (32%)	5 (28%)	13 (52%)	1 (25%)	7 (37%)	34 (37%)
Group 3	7 (28%)	5 (28%)	1 (4%)	0	1 (5%)	14(15%)
Group 4	0	1 (5.5%)	1 (4%)	0	2 (10%)	4 (4%)

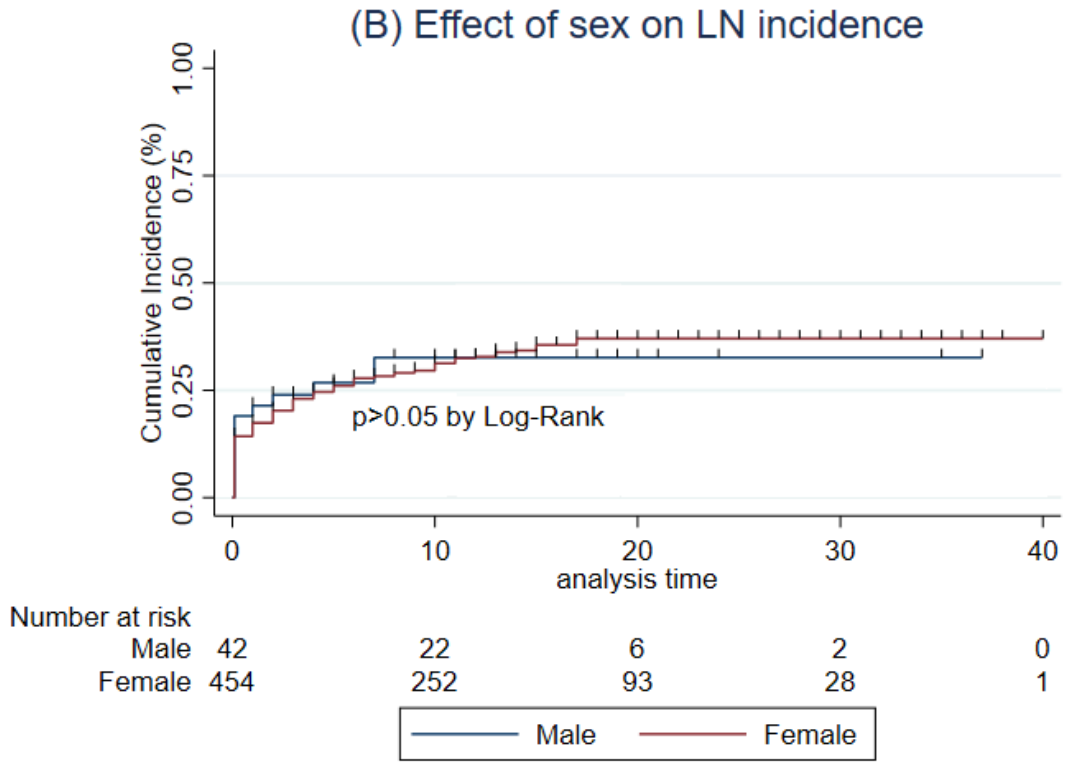
Footnote to Table 2

Other causes of death included suicide (2), road traffic accident (1), old age (1), liver failure (2), unknown cause (5), alcoholism (1), thrombotic thrombocytopaenic purpura (1), haemorrhage (3), haemolytic anaemia (1), acute respiratory distress syndrome (1) and chronic obstructive pulmonary disease (1).

Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keac218/6567344 by University College London user on 19 April 2022

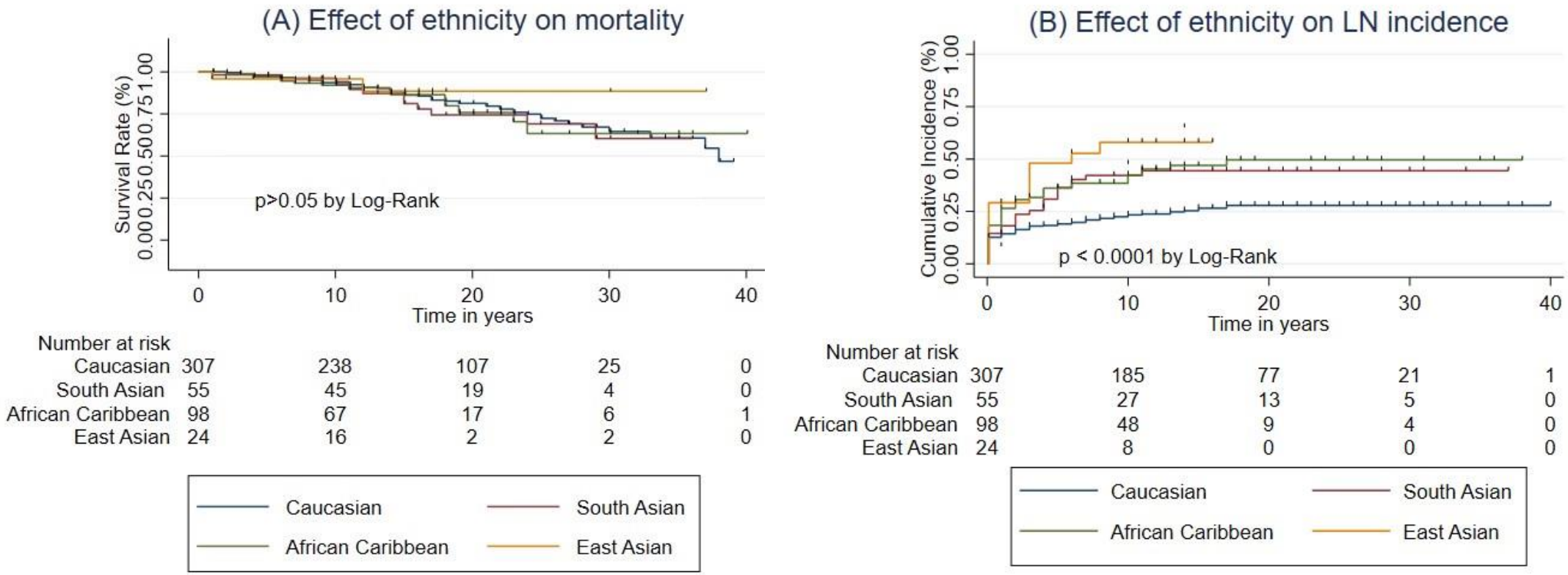
Figure 1. Effect of sex on mortality and LN incidence





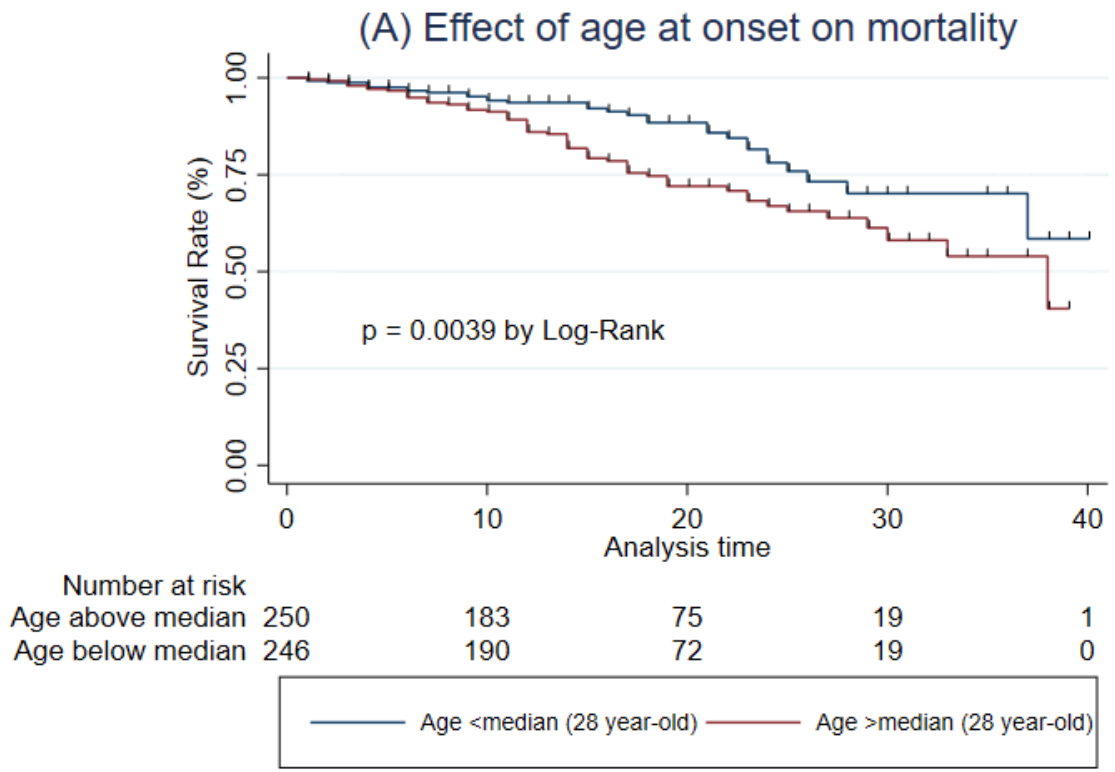
ded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keac218/6567344 by University College London user on 19 A

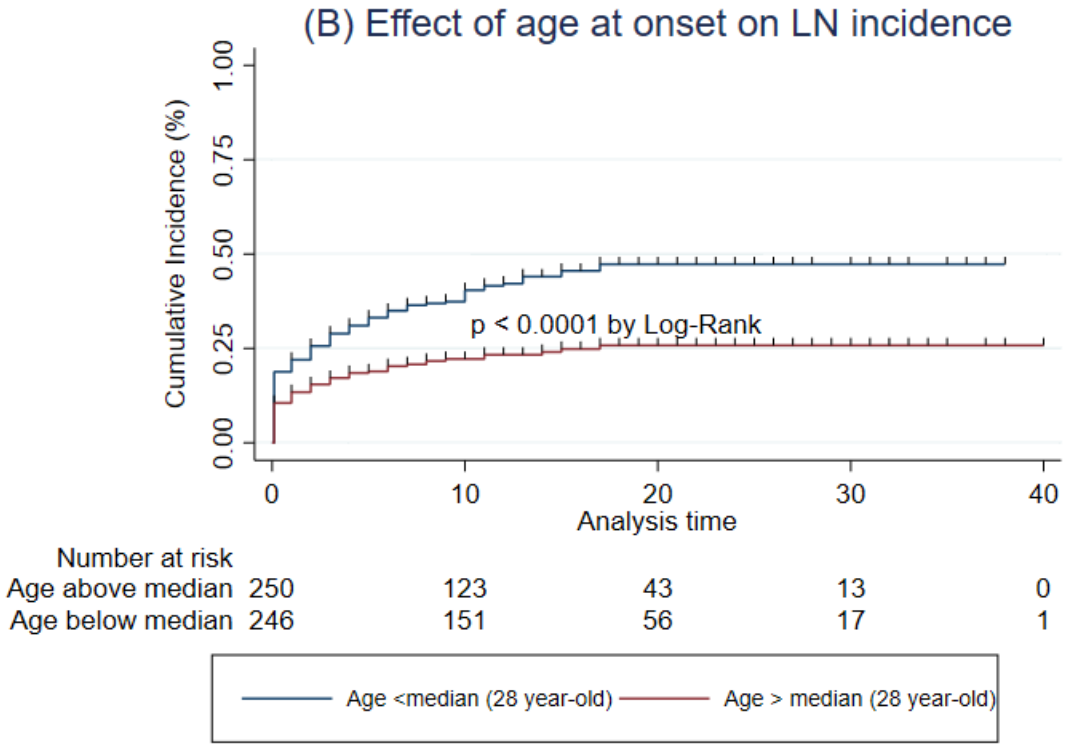
Figure 2. Effect of ethnicity on mortality and LN incidence



Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keac218/6567344 by University College London user on 19 A

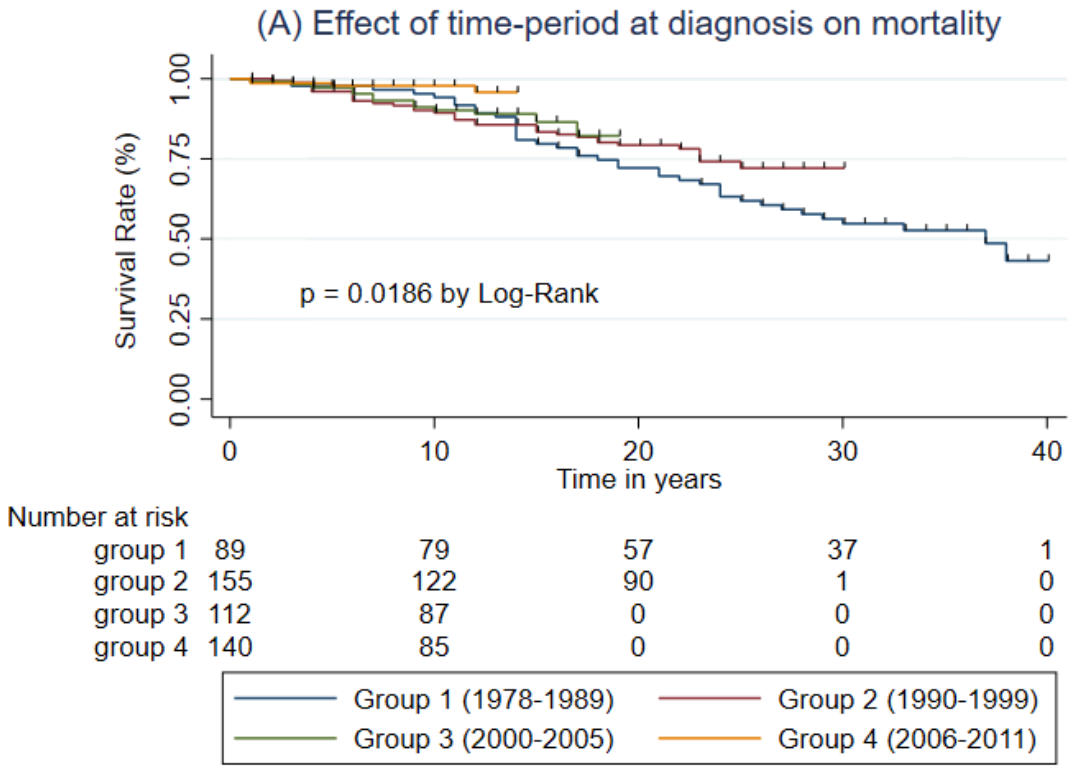
Figure 3. Effect of age at onset on mortality and LN incidence

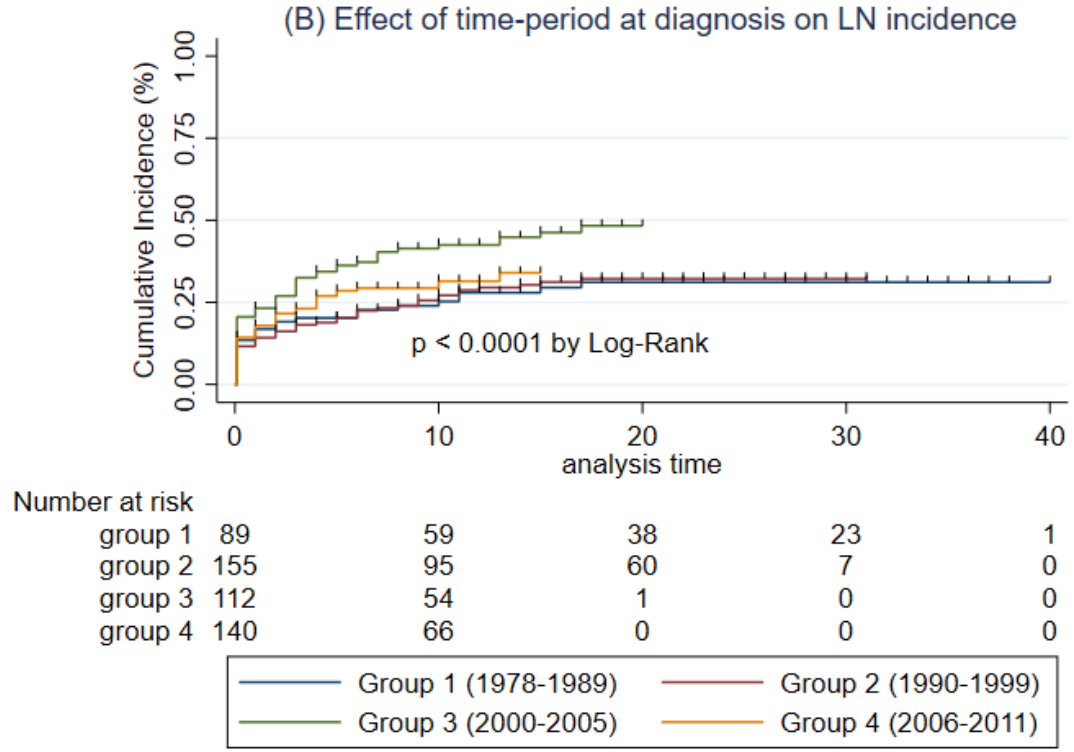




ed from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keac218/6567344 by University College London user on 19 /

Figure 4. Effect of time-period at diagnosis on mortality and LN incidence





Downloaded from https://academic.oup.com/rheumatology/advance-article/doi/10.1093/rheumatology/keac218/6567344 by University College London user on 19 A