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Improved Survival in Granulomatosis with Polyangiitis: A General Population-Based Study

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Abstract

Background—Granulomatosis with polyangiitis (GPA) is associated with an increased risk of mortality; however, recent mortality trends in GPA are unknown. We evaluated this issue in a general population context.

Methods—Using data collected between 1992 and 2013 by The Health Improvement Network in the United Kingdom, we identified individuals diagnosed as incident cases of GPA and up to 10 non-GPA controls matched on sex, age, year of birth, and year of GPA diagnosis. The cohort was divided into two based on the year of diagnosis (i.e., 1992–2002 and 2003–2013) to evaluate changes in mortality. We calculated hazard ratios for death using a Cox-proportional hazards model and the rate differences using an additive hazard model, while adjusting for potential confounders.

Results—We identified 465 cases of GPA (mean age, 60 years; 52% male). The early cohort (1992–2002) GPA patients had considerably higher mortality rates than the late cohort (2003–2013) (i.e., 72.0 versus 35.7 cases per 1000 person-years), as compared with a moderate improvement in the comparison cohorts between the two periods (19.8 versus 17.0 cases per 1000 person-years). The corresponding absolute mortality rate difference was 52.2 (95% CI, 25.1–79.2) cases and 18.7 (95% CI, 8.3–29.1) cases per 1000 person-years (p for interaction=0.025). The resulting HRs for mortality were 4.34 (95% CI, 2.72–6.92) and 2.41 (95% CI, 1.74–3.34), respectively (p for interaction=0.043).

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Ethical approval information: This study was approved by the THIN Scientific Review Committee IRB.

Data sharing statement: At this moment there are no additional unpublished data.

Conclusion—This population-based study suggests that survival of GPA patients has improved considerably over the past two decades, affirming the benefits of recent trends in the management of GPA and its complications.

Keywords

Autoantibody; Granulomatosis with polyangiitis; epidemiology; cyclophosphamide

INTRODUCTION

Granulomatosis with polyangiitis (GPA; formerly Wegener's Granulomatosis (1)) is a type of anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV) typically associated with necrotizing, granulomatous inflammation. It has a predilection for the upper and lower airways as well as the kidneys, where it is a cause of rapidly progressive glomerulonephritis. Prior reports describe higher mortality in patients with GPA (and other forms of AAV) compared to the general population, standardized mortality rate (SMR) estimates ranging from 2.1 to 4.8 (2–9).

The addition of cyclophosphamide to glucocorticoids in the treatment of GPA transformed the prognosis from a uniformly fatal disease to a chronic condition (10, 11), complicated by treatment-related morbidity such as infections and malignancies (4, 11, 12, 13). Over the last two decades, management strategies have tended to minimize cumulative doses of cyclophosphamide (14) in favor of medications such as azathioprine and methotrexate (15–18). The goals of the use of these medications have been two-fold: to decrease the duration of patients' exposure to cyclophosphamide and to minimize the quantity of glucocorticoids required to maintain disease remission. Coincident with these changes, Watts et al. reported an increasing prevalence of GPA that is likely multifactorial, related in part to greater awareness of the disease and improved diagnostic approaches, but also perhaps to improved survival (19).

To date, no study has directly evaluated whether mortality trends have improved over the past several decades, although the management of GPA and its complications has evolved substantially. We sought to address this key knowledge gap in a general population context.

METHODS

Data Source

Data were obtained from The Health Improvement Network (THIN) which includes data on approximately 7.3 million patients derived from 477 general practices in the United Kingdom (UK) (20). Because the National Health Service (NHS) in the UK requires every individual to be registered with a general practitioner (GP) regardless of health status, THIN is a population-based cohort representative of the UK general population. During clinical visits, data on diagnoses, prescription medications, height, weight, smoking status, and other variables are entered by providers. The Read classification is used to code specific diagnoses (21) and a drug dictionary based on data from the Multilex classification is used to code

drugs (<http://www.fdbhealth.com/multiplex-overview/1/26/2015>). This study was approved by the THIN Scientific Review Committee.

Study Design

We performed a matched cohort study to examine the relationship of patients with incident GPA with the risk of all-cause mortality. For each GPA case, we selected up to 10 individuals (without GPA at the index date of GPA onset) and matched them to cases by sex, age, year of birth, and data-entry date (same month and year). The eligible population included all patients aged 20 to 90 years who had been enrolled in the THIN database between 1992 and 2013 for at least one continuous year prior to the index date; those with a previous diagnosis of GPA were excluded. We then divided the cohort into two calendar-time based sub-cohorts, based on the year of diagnosis (i.e., 1992–2002 [early cohort] and 2003–2013 [recent cohort]) to evaluate changes in mortality. These time periods of 11 years were chosen based on the timing of publications between 2000 to 2003 studying the safety and efficacy of reduced cyclophosphamide exposure and steroid-sparing agents (e.g., azathioprine, methotrexate) for maintenance therapy (14, 17). We followed patients included in this study from the date of diagnosis and reference participants from the matched (index) date until occurrence of death, migration out of the THIN database, or December 31, 2013, whichever came first.

Ascertainment of GPA

GPA was defined using Read codes for Wegener's granulomatosis and Wegener's syndrome, a strategy that has been previously validated (19). Cases were defined as those with a first diagnosis of GPA entered into the record during the period from January 1, 1992 through December 31, 2013. The entry date was considered to be the date at which a first diagnosis of GPA was given. A cushion period of a minimum of 1 year was used to identify incident cases of GPA.

Assessment of Covariates

From the THIN database, we collected data on personal characteristics and lifestyle factors such as smoking status, body mass index (BMI), alcohol use, healthcare utilization (i.e., GP visits), social-economic deprivation index (SDI) and comorbidities (i.e., chronic kidney disease, hypertension, stroke, hyperlipidemia, and diabetes). The Charlson Comorbidity Index (CCI) (22) prior to the index date was calculated. BMI, smoking status, and alcohol consumption were recorded to the nearest possible measurement prior to the index date. Similarly, we assessed baseline use of the following medications commonly prescribed to treat cardiovascular disease which have affected mortality rates: angiotensin converting enzyme inhibitors, beta-blockers, aspirin, angiotensin II receptor blockers, and calcium channel blockers. We also assessed baseline use of diuretics, non-steroidal anti-inflammatory drugs, and glucocorticoids.

Statistical Analysis

We compared the baseline characteristics of patients with GPA and the comparison cohort. Person-years of follow up for each patient were computed at the time from the index date to

the end of follow-up. We calculated incidence rates of death for each group by dividing the number of cases of each outcome variable by the number of person-years. The associations between GPA and study outcomes are expressed as incidence rate ratios with 95% confidence intervals (CIs). We used the Kaplan-Meier method to construct estimated survival curves for the two calendar-time based sub-cohorts (i.e., 1992–2002 [early cohort] and 2003–2013 [recent cohort]).

Cox proportional hazard regression models were used to calculate hazard ratios (HRs) for total and sub-cohort follow-ups, after accounting for matched clusters (age, sex, and entry date). Our intermediate multivariate model adjusted for lifestyle factors (smoking, alcohol consumption, BMI), GP visits, and the CCI. The full multivariate model adjusted for all of the above as well as comorbidities and medications assessed prior to the index date. We then tested the significance of interaction between GPA and time period by adding the time period variable and the interaction terms to all models. We also calculated the absolute rate difference using an additive hazard model (23) for the two sub-cohort follow-ups and tested the additive interaction between GPA and time period

As previously described (24), our primary analysis used imputed missing values for covariates (i.e., smoking and alcohol use), employing a sequential regression method based on a set of covariates as predictors (IVEware for SAS, V.9.2; SAS Institute, Cary, North Carolina, USA). To minimize random error, we imputed five datasets and then combined estimates from these datasets (24). We calculated 95% CIs for all HRs. All p values were two-sided.

We used SAS, version 9.2 (SAS Institute, Cary, North Carolina, USA) for all statistical analyses.

RESULTS

Baseline Characteristics

Our study population included 465 patients with GPA and 4,613 patients without GPA. Table 1 shows baseline characteristics of patients in both groups. The average age of patients with GPA was 60.3 years (± 14.6), comparable to other reports of GPA in the UK (18). Patients with GPA tended to have more comorbidities (including lower albumin levels) and greater use of cardiovascular medications, NSAIDs, and glucocorticoids compared with the comparison cohort. Over the course of the study, the number of patients enrolled in the THIN database increased, accounting for the increased number of GPA cases in the more recent cohort.

All-Cause Mortality During the Entire Follow-Up Period (1992–2013)

There were 101 deaths in the GPA group (N=465) compared to 511 in the comparison cohort (N=4613) (Table 2). The incidence rate of death (per 1000 person-years) in the GPA group was 43.5 (95% CI, 35.4–52.9) compared to 19.3 (95% CI, 17.6–21.0) in the comparison cohort (Figure 1a). The age-, sex-, and entry time-matched HR for mortality among GPA patients was 2.76 (95% CI, 2.19–3.47). The HR for mortality remained significant, after adjusting for potential confounders (2.52; 95%, 1.91–3.32).

Overall, the HR of death was similar among male and female patients in the fully adjusted models. Among female patients the HR was 2.22 (95%, 1.45–3.38) compared to 2.87 (95%, 1.96–4.20) in male patients. Similarly, there was no apparent difference in the mortality HR between those older and younger than 65 years of age. Patients over 65 years old had a HR of 2.37 (95%, 1.69–3.34) compared to 2.52 (95% 1.51–4.19) among younger patients.

With regard to the timing of death, patients with GPA were at the greatest risk of death in the first year following diagnosis (Figure 1a, Table 3). The incidence rate for death in the first year was 97.4 (96% CI, 69.6–132.6) per 1000 person-years compared to 42.5 (95% CI, 34.2–52.1) over the ten years following diagnosis. In the fully-adjusted model, the HR for mortality in the first year was 6.31 (95% CI, 3.62–10.98) compared to 2.51 (95% CI, 1.88–3.36) over the ten years following diagnosis. Although still elevated, the risk of death of GPA declined towards that of the general population in the years following diagnosis.

Mortality Trends Over Calendar-Time

Figure 1b shows the survival rate of patients during the follow up according to the calendar-year based sub-cohort. The early cohort (1992–2002) GPA patients had considerably higher mortality rates than the recent cohort (2003–2013) patients (72.0 vs. 35.7 cases per 1000 person-years; Table 4), as compared with a moderate improvement in mortality rates in the comparison cohorts between the two periods (19.8 vs 17.0 cases per 1000 person-years). The corresponding absolute mortality rate difference was 52.2 (95% CI, 25.1–79.2) cases and 18.7 (95% CI, 8.3–29.1) cases per 1000 person-years (p for interaction=0.025). When matched for age, sex, and entry-time, the HR for mortality was 4.34 (95%, 2.72–6.92) in the early cohort in contrast to 2.41 (95%, 1.74–3.34) in the recent cohort (p for interaction = 0.043). In the intermediate multivariate model adjusted for lifestyle factors (smoking, alcohol consumption, BMI), SDI, GP visits, and the CCI, the HR remained elevated in the early cohort (3.73, 95%, 2.11–6.61) compared to that of the recent cohort (2.51, 95%, 1.75–3.59). In the fully adjusted multivariate model adjusting for comorbidities and medications, the HR was 3.54 (95%, 1.73–7.24) in the early cohort and 2.46 (95%, 1.67–3.64) in the recent cohort.

DISCUSSION

Granulomatosis with polyangiitis (GPA) is a severe, life threatening form of small-vessel vasculitis previously associated with increased mortality due to the disease itself as well as due to complications of treatment (6, 10–13, 18). In this large general practice cohort representative of the UK population, we confirm the observation that GPA is associated with increased mortality, especially in the first year following diagnosis. Furthermore, the survival of GPA patients has improved considerably over the past two decades, although the mortality in the recent cohort (2003–2013) was still higher than that in non-GPA patients. These trends were evident in both ratio and difference measures, as compared with the background mortality improvement over the years. These findings provide the first population-based evidence for the benefits of improved GPA care over the past two decades. A prior study by Takala et al found no difference over time when examining the two decades

spanning 1981–2000 (7). While these data are encouraging, our data also indicate a notably increased risk of premature mortality in GPA patients even over the past decade.

Our findings suggest that trends in the management of GPA that have emphasized less cumulative cyclophosphamide exposure and greater use of azathioprine and other steroid-sparing agents may have had a favorable impact on survival. Prior reports have described an increased risk of cardiovascular disease and malignancy in patients with GPA (3, 25, 26); thus, advances in the management of these conditions may also account for some of the increased survival we observed in the later cohort. Other secular trends in the management of infectious, renal, and pulmonary complications – of which ANCA patients are at an elevated risk – may have also influenced the trend in mortality. Our results suggest that differences in mortality between the recent and early cohorts may be driven more by improved survival after the first year of diagnosis (Figure 1b). This may support our hypothesis that shifts in management might drive the improved survival since many of the complications of treatment (e.g., infection, secondary malignancy) occur after prolonged exposure. Additionally, improvements in the management of complications (e.g., infection, renal disease) may impact late survival. Yet, the remaining increased mortality risk, especially early in the disease course, calls for further improvement in GPA care.

The overall adjusted HR of mortality in our cohort appears to be somewhat lower (2.5; 95% CI, 1.90–3.28) than nearly all prior reports (2–9). One explanation for this is the nature of the THIN database, which includes diagnoses made in both inpatient and outpatient settings, thus enriching our dataset with patients of varying disease severity. Another explanation is the inclusion of patients diagnosed after 2004, a period characterized by improved survival which has not been evaluated in previous studies. Indeed, the mortality rate in the early cohort is very similar to that reported by Takala et al. in their retrospective (1981–2000) cohort study using a Finnish hospital discharge registry (7); that study used age- and sex-matched controls from the same practice as the case. Furthermore, although we used person-time based mortality rates (i.e., a preferred option in observational studies such as ours) as our risk estimate, the proportion of deaths during our early cohort follow-up closely agreed with a previous UK GP data-based study (9) whose period (1989–2004) coincided well with our early cohort follow-up time (1992–2002). That previous UK study showed 21% deaths in the GPA cohort vs. 7.8% in the control cohort, whereas the corresponding proportions in our study were 21% and 7%, respectively (calculated based on the data in Table 4). Nevertheless, we did not observe any significant difference in the mortality rate among male and female patients unlike prior reports (4, 7, 8, 11, 13, 27). Similarly, being over the age of 65 years did not confer a significantly increased risk of death in our cohort, which contrasts with previous observations (8, 27).

Our study has several strengths. It is one of the largest studies evaluating mortality due to GPA in a population-based cohort and includes patients diagnosed after 2004, a period not previously studied. The diagnosis and management of GPA has changed significantly between 1992 and 2013 with a wider availability of ANCA testing to assist with diagnosis (28) and trends toward lower cumulative cyclophosphamide doses and the increased use of conventional steroid-sparing agents such as azathioprine and methotrexate for maintenance therapy (14–18). The extended period covered in this study allowed us to evaluate mortality

in the setting of these trends in management. In contrast to Takala et al. (7), the inclusion of GPA cases diagnosed in our general population context limited bias towards the more severe cases typically admitted to hospitals and makes our findings more generalizable. The relative recent approval in the UK of rituximab for remission induction in GPA means that the impact of this new treatment could not be evaluated in this study.

Despite these strengths, our study has limitations. Our study relied on physician diagnosis of GPA, which was not confirmed according to pre-specified criteria. However, prior studies have confirmed the validity of Read codes for GPA according to the American College of Rheumatology criteria and the Chapel Hill Consensus Conference definition (19). We did not have sufficient detail on the cause of death in a number of cases in our dataset, precluding investigations on the cause of death in this cohort. Nevertheless, the overall all-cause mortality trends are critically important in their own right. Future studies should address potential specific reasons behind this improvement, including changes in specific therapeutics (including the recent use of rituximab (29)), the data of which are generally incomplete in our GP practice-based database.

CONCLUSIONS

In conclusion, we found that mortality is increased among individuals with GPA, even in the most recent cohort (2003–2013). Further, our findings provide the first population-based evidence for a considerable trend toward improved survival over the past two decades. These data affirm the benefits of recent trends in the management of GPA and its complications.

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Figure 1.
Survival According to the Presence of Granulomatosis with Polyangiitis

Table 1

Baseline Characteristics According to the Presence of Granulomatosis with Polyangiitis

Variables	Granulomatosis with Polyangiitis (n=465)	Comparison Cohort (n=4613)	P
Age, years	60.3 ± 14.6	60.3 ± 14.6	0.95
Sex			
Male	245 (52.7%)	2419 (52.4%)	0.92
Female	220 (47.3%)	2194 (47.6%)	
BMI (kg/m²)			0.76
Mean ± SD	26.8 ± 5.1	26.9 ± 5.2	
<18.5	13 (2.8%)	59 (1.3%)	
18.5–24.9	132 (28.4%)	1390 (30.1%)	
25.0–29.9	145 (31.2%)	1435 (31.1%)	
30.0	86 (18.5%)	828 (17.9%)	
Unknown	89 (19.1%)	901 (19.5%)	
Socio-Economic Deprivation Index Score	2.6 ± 1.4	2.6 ± 1.4	0.78
Smoking			0.01
None	229 (49.2%)	2310 (50.1%)	
Past	128 (27.5%)	993 (21.5%)	
Current	70 (15.1%)	830 (18.0%)	
Unknown	38 (8.2%)	480 (10.4%)	
Alcohol			0.58
None	72 (15.5%)	663 (14.4%)	
Past	10 (2.2%)	67 (1.5%)	
Current	298 (64.1%)	2993 (64.9%)	
Unknown	85 (18.3%)	890 (19.3%)	
Charlson Comorbidity Index	0.7 ± 1.2	0.3 ± 0.9	<0.001
GP Visits	6.1 ± 4.3	3.0 ± 3.5	<0.001
Hypertension	144 (31.0%)	1303 (28.2%)	0.22
Hyperlipidemia	95 (20.4%)	898 (19.5%)	0.62
Stroke	30 (6.5%)	196 (4.2%)	0.03
Ischemic Heart Disease	45 (9.7%)	403 (8.7%)	0.50
Chronic Kidney Disease	63 (13.5%)	185 (4.0%)	<0.001
Diabetes	24 (5.2%)	326 (7.1%)	0.12
Angiotensin Converting Enzyme Inhibitor	69 (14.8%)	630 (13.7%)	0.48
Aspirin	74 (15.9%)	627 (13.6%)	0.17
Angiotensin II Receptor Blockers	21 (4.5%)	218 (4.7%)	0.84
Beta-Blockers	69 (14.8%)	599 (13.0%)	0.26
Calcium Channel Blockers	82 (17.6%)	545 (11.8%)	<0.001
Diuretics	111 (23.9%)	714 (15.5%)	<0.001

Variables	Granulomatosis with Polyangiitis (n=465)	Comparison Cohort (n=4613)	P
NSAIDs	160 (34.4%)	846 (18.3%)	<0.001
Glucocorticoids	182 (39.1%)	203 (4.4%)	<0.001
Albumin, mmol/L	37.0 ± 6.3	42.3 ± 3.7	<.0001
Cholesterol, mmol/L	5.0 ± 1.3	5.2 ± 1.1	0.03

Data are represented as mean ± standard deviation (SD) or number (percentage); Socio-Economic Deprivation Index score was measured by the Townsend Deprivation Index, which was grouped into quintiles from 1 (least deprived) to 5 (most deprived); Hyperlipidemia is defined as having either a diagnosis of hyperlipidemia or a prescription for antihyperlipidemics; Glucocorticoids are oral or injectable steroids; Diuretics are loop or thiazide diuretics.

Incidence Rates and Hazard Ratios (HR) for Associations Between Granulomatosis with Polyangiitis (GPA) and Death (1992–2013)

Table 2

	GPA Status	N	Deaths	Follow-up Time (person-years)	Mean Follow-up (years)	Incidence Rate (cases per 1000 person-years)	Age, Sex, and Entry-time Matched HR (95%CI)*	+ GPs visits, BMI, SDI, Smoking, Alcohol, and Charlson Index Adjusted HR (95%CI)	+ Comorbidity and Medicines Adjusted HR* (95%CI)
Total	Yes	465	101	2321.5	5.0	43.51 (35.44 to 52.86)	2.76 (2.19 to 3.47)	2.64 (2.07 to 3.38)	2.52 (1.91 to 3.32)
	No	4613	511	26521.4	5.7	19.27 (17.63 to 21.01)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Female	Yes	220	38	1182.7	5.4	32.13 (22.74 to 44.10)	2.20 (1.54 to 3.16)	2.31 (1.57 to 3.39)	2.22 (1.45 to 3.38)
	No	2194	235	13097.2	6.0	17.94 (15.72 to 20.39)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Male	Yes	245	63	1138.9	4.6	55.32 (42.51 to 70.77)	3.27 (2.42 to 4.41)	2.86 (2.06 to 3.96)	2.87 (1.96 to 4.20)
	No	2419	276	13424.2	5.5	20.56 (18.21 to 23.13)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Age < 65	Yes	275	32	1603.7	5.8	19.95 (13.65 to 28.17)	3.13 (2.07 to 4.72)	2.75 (1.76 to 4.30)	2.52 (1.51 to 4.19)
	No	2730	116	16683.1	6.1	6.95 (5.75 to 8.34)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Age > 65	Yes	190	69	717.9	3.8	96.11 (74.78 to 121.64)	2.61 (1.98 to 3.44)	2.57 (1.91 to 3.46)	2.37 (1.69 to 3.34)
	No	1883	395	9838.3	5.2	40.15 (36.29 to 44.31)	1.0 (reference)	1.0 (reference)	1.0 (reference)

* Adjusted for all of the covariates in Table 1

Incidence Rates and Hazard Ratios (HR) for Associations Between Granulomatosis with Polyangiitis (GPA) and Death According to Different Follow Up Time Period

Table 3

	GPA Status	N	Deaths	Follow-up Time (person-years)	Mean Follow-up (years)	Incidence Rate (cases per 1000 person-years)	Age, Sex, and Entry-time Matched HR (95%CI) *	+ GP's visits, BMI, SDI, Smoking, Alcohol, and Charlson Index Adjusted HR * (95%CI)	+ Comorbidity and Medicines Adjusted HR * (95%CI)
Overall	Yes	465	101	2321.5	5.0	43.51 (35.44 to 52.86)	2.76 (2.19 to 3.47)	2.64 (2.07 to 3.38)	2.52 (1.91 to 3.32)
	No	4613	511	26521.4	5.7	19.27 (17.63 to 21.01)	1.0 (reference)	1.0 (reference)	1.0 (reference)
0-1 year	Yes	465	40	410.7	0.9	97.39 (69.58 to 132.62)	6.67 (4.44 to 10.00)	6.85 (4.21 to 11.15)	6.31 (3.62 to 10.98)
	No	4613	62	4344.8	0.9	14.27 (10.94 to 18.29)	1.0 (reference)	1.0 (reference)	1.0 (reference)
0-3 years	Yes	465	61	1050.8	2.3	58.05 (44.40 to 74.57)	3.66 (2.72 to 4.94)	3.54 (2.56 to 4.90)	3.35 (2.31 to 4.85)
	No	4613	196	11477.0	2.5	17.08 (14.77 to 19.64)	1.0 (reference)	1.0 (reference)	1.0 (reference)
0-5 years	Yes	465	72	1531.2	3.3	47.02 (36.79 to 59.22)	3.03 (2.32 to 3.97)	2.94 (2.21 to 3.92)	2.78 (2.01 to 3.84)
	No	4613	290	16702.2	3.6	17.36 (15.42 to 19.48)	1.0 (reference)	1.0 (reference)	1.0 (reference)
0-10 years	Yes	465	91	2143.5	4.6	42.45 (34.18 to 52.12)	2.66 (2.10 to 3.38)	2.61 (2.02 to 3.37)	2.51 (1.88 to 3.36)
	No	4613	442	23807.0	5.2	18.57 (16.88 to 20.38)	1.0 (reference)	1.0 (reference)	1.0 (reference)

* Adjusted for all of the covariates in Table 1

Incidence Rates and Hazard Ratios (HR) for Associations Between Granulomatosis with Polyangiitis (GPA) and Death According to Calendar Time-Based Subgroups (1992–2002 vs. 2003–2013)

Table 4

	GPA Status	N	Deaths	Follow-up Time (person-years)	Mean Follow-up (years)	Incidence Rate (cases per 1000 person-years)	Age, Sex, and Entry-time Matched HR (95%CI)*	+ GPs visits, BMI, SDI, Smoking, Alcohol, and Charlson Index Adjusted HR (95%CI)	+ Comorbidity and Medicines Adjusted HR* (95%CI)
Total	Yes	465	101	2321.5	5.0	43.51 (35.44 to 52.86)	2.76 (2.19 to 3.47)	2.64 (2.07 to 3.38)	2.52 (1.91 to 3.32)
	No	4613	511	26521.4	5.7	19.27 (17.63 to 21.01)	1.0 (reference)	1.0 (reference)	1.0 (reference)
1992–2002	Yes	127	27	374.9	3.0	72.02 (47.46 to 104.78)	4.34 (2.72 to 6.92)	3.73 (2.11 to 6.61)	3.54 (1.73 to 7.24)
	No	1251	85	4296.5	3.4	19.78 (15.80 to 24.46)	1.0 (reference)	1.0 (reference)	1.0 (reference)
2003–2013	Yes	338	47	1316.4	3.9	35.70 (26.23 to 47.48)	2.41 (1.74 to 3.34)	2.51 (1.75 to 3.59)	2.46 (1.67 to 3.64)
	No	3362	244	14339.7	4.3	17.02 (14.95 to 19.29)	1.0 (reference)	1.0 (reference)	1.0 (reference)

* Adjusted for all of the covariates in Table 1