Higher Total White Blood Cell and Neutrophil Counts Are Associated With Increased Stroke Mortality Risk: The Guangzhou Biobank Cohort Study

Zhi-bing. Hu
Guangzhou Twelfth People's Hospital, Guangzhou

Ze-xiong Lu
Guangzhou Twelfth People's Hospital, Guangzhou

Feng Zhu (chifengzhu@hotmail.com)
Guangzhou Twelfth People's Hospital, Guangzhou

Cao-qiang Jiang
Guangzhou Twelfth People's Hospital, Guangzhou

Wei-sen Zhang
Guangzhou Twelfth People's Hospital, Guangzhou

Jin Pan
Guangzhou Twelfth People's Hospital, Guangzhou

Ya-li Jin
Guangzhou Twelfth People's Hospital, Guangzhou

Lin Xu
Sun Yat-sen University

G. Neil Thomas
University of Birmingham

Karkeung Cheng
University of Birmingham

Taihing Lam
University of Hong Kong

Research Article

Keywords: stroke, WBC, neutrophil, mortality, cohort

DOI: https://doi.org/10.21203/rs.3.rs-253533/v1

License: © This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
Abstract

Background: To investigate the relations of white blood cell (WBC) count and its dynamic change with future stroke mortality risk in a relatively healthy elderly population.

Methods: A total of 27811 participants without stroke history at baseline were included and followed up for an average of 11.5 (SD=2.3) years. After review of available records, 399 stroke (277 ischaemic and 172 haemorrhagic) deaths were recorded among all-cause mortality. Cox proportional hazards regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs).

Results: Compared with the lowest quartile, the highest quartile of WBC count showed 53% and 67% increased mortality risk for total (adjusted HR [aHR]=1.53, 95% CI 1.16-2.02, P=0.003) and haemorrhagic stroke (aHR=1.67, 95% CI 1.10-2.67, P=0.03) and haemorrhagic stroke, respectively; the highest neutrophil count showed 45% and 65% increased mortality risk for total (aHR=1.45, 95% CI 1.10-1.89, P=0.008) and ischaemic (aHR=1.65, 95% CI 1.10-2.47 P=0.02) stroke. The same results found for total and ischaemic stroke but not for haemorrhagic stroke were observed for both WBCs and neutrophils within the normal range level after further C-reactive protein (CRP) adjustment. Compared with the stable group, the 25% increased groups of both WBCs (aHR=1.60, 95% CI 1.07-2.40, P=0.02) and neutrophils (aHR=1.45, 95% CI 1.02-2.05, P=0.04) showed 60% and 45% increased stroke mortality risk, respectively.

Conclusions: These findings support the role of WBCs, especially neutrophils, as simple, inexpensive and readily available predictors of future stroke mortality in an elderly population.

Trial registration: The Guangzhou Medical Ethics Committee of the Chinese Medical Association approved the study.

Background

Stroke is mainly categorized as ischaemic and haemorrhagic [1], 1989 #2. With a high prevalence of comorbidities in developed Western countries, pre-existing chronic low-grade systemic inflammation has become a recognized characteristic of stroke pathophysiology [2]. Evidence now suggests that a chronic inflammatory response has been associated with an increased risk of ischaemic [3, 4] and haemorrhagic [5] stroke. Total white blood cell count (WBC), a plausible marker in the pathogenesis of chronic inflammation [6], is generally conducive to stroke incidence.

Increased WBC count on admission was linked to poor outcome and increased mortality for patients with total [7, 8], ischaemic [9] and haemorrhagic [10] stroke in case-control studies. However, these WBC counts may be due to the stress reaction in acute patients with stroke [2], and it is not clear that such increased WBC counts are linked directly to stroke mortality. On the other hand, a relatively high WBC count was related to the incidence, unfavourable functional outcome and mortality risk of total [11-15] and ischaemic stroke [13, 15-20] in prospective cohort studies, although there are still controversies regarding total [21], ischaemic [22, 23] and haemorrhagic [15, 19] stroke. Neutrophils (NEUs), the largest WBC subpopulation, showed similar associations with total [8, 15], ischaemic [15, 19, 20, 24-26] and haemorrhagic [27] stroke. However, different types of inflammation can result in increases in not only leucocytes but also other indicators, such as C-reactive protein (CRP). CRP, a controversial independent stroke risk factor and an underlying acute inflammatory risk factor [2], was reported to be a predictor in total [13, 28] and ischaemic [23, 26, 29, 30] stroke in addition to haemorrhagic stroke. Nevertheless, no changes in WBCs or their subpopulations have been reported to be linked with stroke mortality risk to date.

In previous work, we reported that a higher WBC count was associated with all-cause, CHD and respiratory mortality [14], cardiovascular disease [31] and metabolic syndrome risk [32] in the Guangzhou Biobank Cohort Study (GBCS). Here, we aimed to systematically assess the relations of WBCs, their subpopulations and their changes with stroke mortality risk in a healthy elderly population.

Methods

Subjects

All GBCS participants were recruited from among Guangzhou permanent residents aged 50 years or older in southern China. Details of the GBCS have been reported previously [33]. The baseline (from September 2003 to February 2008) and follow-up information included a face-to-face computer-assisted interview by trained nurses on lifestyle [34], family and personal medical history and assessment of anthropometric data, blood pressure and laboratory tests. An appointment had been made for each participant in advance to ensure good health and for each of them to report in person to the designated place to sit and rest for at least half an hour before sampling and examination.

Exposure indicators

WBC and subpopulation counts were performed by a blood cell counter (KX-21, Sysmex, Japan) in Guangzhou Twelfth People's Hospital. WBCs, NEUs and lymphocytes (LYMs) were counted separately, while monocytes, eosinophils and basophils were counted as a mixture. Fasting glucose, cholesterol, triglycerides, liver and kidney function and CRP were measured by an analyser (Cobas c-311, Roche, Switzerland). The hospital laboratory performs internal and external quality control procedures according to the China Association of Laboratory Quality Control.

Study outcomes

Information on underlying causes of death up to December 2017 were mostly obtained via record linkage with the Guangzhou Centre for Disease Control and Prevention (GZCDC). Due to the lack of any other information on stroke severity, infarct volume, site of lesion and infectious complications, mortality was chosen as a primary outcome in this study. Death causes were coded according to the 10th revision of the International Classification of Diseases (ICD) as follows: I60-I69 for total stroke; I60.0-I62.9 and I69.0-I69.2 for haemorrhagic stroke; and I63.0-I63.9 and I69.3 for ischaemic stroke. When the death...
certificates were not issued by medical institutions, the causes were verified by GZCDC as part of their quality assurance programme by cross-checking past medical history and conducting a verbal autopsy by 5 senior clinicians from Guangzhou Twelfth People's Hospital and the Universities of Hong Kong, China and Birmingham, UK.

**Statistical analysis**

WBCs and NEUs were classified by quartiles. WBC and NEU change analyses were categorized into 2 models: ±10% and ±25%. Continuous variables were described by the mean ± standard deviation, and categorical variables were described by frequency and percentage. The chi-square test and Fisher’s exact test were used for categorical variables, and analysis of variance (ANOVA) and the Kruskal-Wallis test were used for continuous variables. The covariates included sex, age, education, occupation, smoking habit, alcohol consumption, physical activity, body mass index (BMI, defined as weight in kg ÷ height in m2) [35], self-rated health, hypertension, diabetes, dyslipidaemia, cancer, genitourinary disease, chest disease, platelet count (continuous) and CRP (continuous). A sensitivity analysis was conducted, including the association between leucocytes and stroke mortality in those with normal WBC levels and after excluding those with NEU levels in the top 1% and bottom 1% at baseline. All analyses were performed using STATA (Version 14.0; StataCorp LP, College Station, TX, USA). All p values were 2 sided, and statistical significance was defined as p < 0.05.

**Results**

**Baseline characteristics**

Of 30,430 participants, 286 were excluded because of previous history of stroke; 315, because of unclear stroke history; 372, because of loss to follow-up with unknown vital status; and 1646, because of incomplete information on WBCs, NEUs, lymphocytes and platelets, hypertension, diabetes, dyslipidaemia, smoking habit, alcohol consumption, physical activity, BMI, self-rated health, cancer, genitourinary disease or chest disease. Thus, 27,811 participants were enrolled in this study. After an average follow-up of 11.5 (SD=2.3) years, 399 stroke deaths (227 ischaemic and 172 haemorrhagic) were recorded.

Table 1 shows basic characteristics at baseline. Compared with those in the 1st quartile, participants from the 2nd to the 4th quartiles included more men, were older, had more manual and former or current smokers and drinkers. Furthermore, these subjects were more likely to have BMI ≥24 kg/m2, hypertension, diabetes and dyslipidaemia; higher levels of NEUs, LYM, platelets and CRP; lower education levels and reduced physical activity and were less likely to have good or very good self-reported health, cancer and genitourinary disease (all P<0.001) compared with those in the 1st WBC quartile.

**WBC in relation to stroke mortality**

The left side of Table 2 shows that an higher WBC count is related to an increased stroke mortality risk. After adjustment for a series of factors, participants in the 4th WBC quartile (>7.2*10^9/L) showed increased mortality risks of total (aHR=1.53, 95% CI 1.16-2.02, P=0.003) and haemorrhagic (aHR=1.67, 95% CI 1.05-2.67, P=0.03) stroke in addition to ischaemic stroke (aHR=1.45, 95% CI 0.96-2.18, P=0.08) compared to participants in the 1st WBC quartile (<5.3*10^9/L). Those in the 2nd, 3rd and 4th WBC quartiles showed an increasing risk trend for total (P<0.001), ischaemic (P=0.01) and haemorrhagic (P=0.02) stroke. The middle of Table 2 shows NEUs in four quartiles. Significant associations with increased mortality risks were observed in total (aHR=1.45, 95% CI 1.10-1.89, P=0.008) and ischaemic (aHR=1.65, 95% CI 1.10-2.47, P=0.02) stroke. Unlike WBCs, neither an increased haemorrhagic mortality risk (aHR=1.14, 95% CI 0.74-1.75, P=0.56) nor an increasing risk trend (P=0.26) for NEU quartiles were observed. When excluding participants with stroke and further CRP adjustment among the 10,041 participants with normal WBCs (4~10*10^9/L), a significant association of those in the 4th quartile was shown only in total stroke (further adjusted HR [fHR]=1.57, 95% CI 1.02-2.42, P=0.04), and an increasing risk trend was found in both total stroke (P=0.012) and ischaemic stroke (P=0.02) (left side of Table 3). When excluding participants with NEU counts in the top 1% and bottom 1% and after further CRP adjustment, the results from 9,946 participants with normal WBC levels indicated that the highest NEU quartile was related to an increased mortality risk for both total (fHR=1.55, 95% CI 1.00-2.41, P=0.05) and ischaemic (fHR=2.47, 95% CI 1.24-4.93, P=0.01) stroke and an increasing risk trend for both total (P=0.009) and ischaemic (P=0.004) stroke; however, NEUs showed neither a significant association with the highest quartile (P=0.18) nor an increasing risk trend (P=0.40) in haemorrhagic stroke (right side of Table 3).

Additionally, LYM showed only a decreased risk trend for ischaemic stroke (P for crude HR [cHR] =0.03). No significant associations of stroke mortality risks with CRP were observed (Table 4).

**WBC changes in relation to stroke mortality**

Table 5 shows the association between stroke mortality risk and changed leucocytes during the period of baseline (from September 2003 to February 2008) to the 1st follow-up (from March 2008 to December 2012). Compared to those with stable disease, participants with WBC or NEU changes within 10% showed no significant mortality risk for total stroke. Once the change reached 25%, a significant mortality risk for total stroke was shown with both increased WBCs (aHR=1.60, 95% CI 1.07-2.40, P=0.02) and increased NEUs (aHR=1.45, 95% CI 1.02-2.05, P=0.04).

**Discussion**

In this study, we found that both WBCs and NEUs were associated with the mortality risk of total stroke, and a higher NEU count was associated with an increased mortality risk of ischaemic stroke in a relatively healthy elderly population. These associations were independent of age, sex, education, occupation, hypertension, diabetes, dyslipidaemia, smoking habit, alcohol consumption, physical activity, BMI, self-rated health, cancer, genitourinary disease, chest disease, platelets and C-reactive protein.
Growing studies on the relationship between leucocytes and stroke have focused mainly on the population at admission after stroke onset. Most of them support that an increased WBC count is related to a poor outcome or mortality [8-10, 15, 26, 27, 36, 37], except for a few cases of disagreement of initial stroke severity [10, 15, 30, 38]. This indicates that inflammation arises together with stroke or that stroke itself leads to leucocytosis, resulting in poor outcomes. In a review [2], a series of biomarkers, such as cytokines, WBCs, CRP and interleukin 6 (IL-6), were shown to participate specifically in stroke progression [39]. When focusing on specific types of inflammation in mice, allergens (anaphylaxis) were found to induce IL-10 and a corresponding response, while endotoxin (lipopolysaccharide, LPS) was shown to stimulate various types of cells including leucocytes to induce the release of a series of active molecules [40]. This is evidence for the different types of inflammation involved in stroke progression.

We present a corresponding relation of stroke mortality risks with pre-existing chronic low-grade systemic inflammation. For the GBCS to collect a series of data from relatively healthy elderly individuals in South China, each appointment was made in advance to ensure good health and for each participant to be able to report in person to the designated place [32, 41, 42]. In addition, we excluded those with WBC levels at the top and bottom to avoid intervention in acute inflammatory reactions. Our results are consistent with some previous reports [11, 13, 14] showing that a higher WBC count is related to an increased total stroke mortality risk. The results were reaffirmed after further CRP adjustment, similar to reports from the Japan Collaborative Cohort Study [28] and the Glasgow Inflammation Outcome Study [43]. Unlike the reports of incongruent factors [15-20], we found WBC quartiles to have an increased risk trend for ischaemic stroke; such a weak association may be due to our additional adjustments. Nevertheless, a similar association with haemorrhagic stroke disappeared after further adjustments.

As the largest subpopulation, NEUs play an important role in the major processes of atherosclerosis, thrombosis and stroke [44]. Our results are consistent with a few previous publications [15, 19, 20] and are in contrast with a number of others [45-53] that show a higher NEU count in relation to the increased mortality risk for both total and ischaemic stroke. Taking into account WBCs and NEUs in stroke, our findings suggest that NEUs are more relevant for predicting future stroke mortality.

CRP has been reported as an independent risk factor in clinical stroke [9, 26, 30]. Here, we observed no significant relationship between CRP and stroke mortality risk (Table 4). This is likely because our analytic data was collected from relatively healthy participants.

There are different leucocyte backgrounds in individuals, and each can reach 15% fluctuation in one day [54]. Stroke events are related to chronic inflammation, while leucocytes can well explain the immediate inflammatory status. Here, we used the data from baseline to the first follow-up and guaranteed the stability of leucocyte counts because each participant sat and rested for at least half an hour before sampling and examination. We report first the total stroke mortality risk in relation to changes in WBCs and NEUs in healthy elderly Chinese individuals. This indicates that an increase in leucocytes, a relatively long-term or continuous chronic inflammation, promotes a higher stroke mortality risk.

**Conclusions**

Higher WBC and neutrophil counts were associated with increased stroke mortality risk. Neutrophils were more relevant to predicting future stroke mortality in a healthy elderly population.

**Abbreviations**

WBC: white blood cell count; HR: hazard ratio; aHR: adjusted HR; cHR: crude hazard ratio; CI: confidence interval; NEU: neutrophil; CRP: C reactive protein; LYM: lymphocyte; GBCS: Guangzhou Biobank Cohort Study; GZCDC: Guangzhou Centre for Disease Control and Prevention; ICD: International Classification of Diseases

**Declarations**

**Ethics approval and consent to participate**

Our study was approved by the Guangzhou Medical Ethics Committee of the Chinese Medical Association, and all participants provided written informed consent before participation in the GBCS. The methods of this study were performed in accordance with the Declaration of Helsinki.

**Consent for publication**

Not applicable

**Availability of data and materials**

The datasets used during the current study are available from the corresponding author on reasonable request.

**Competing interests**

The authors declare that they have no competing interests.

**Funding**

This work was supported by the Guangzhou Science and Technology Bureau, Guangzhou, China (201704030132; 2013J4100031; 2012JS100041; 200222-E2051) and the University of Birmingham, UK.
Authors’ contributions

CQJ contributed to the study design. ZBH, ZXL, YLJ, JP and WSZ contributed to data collection and analysis. FZ and ZXL wrote the manuscript. GNT, LX, KKZ and TL reviewed the manuscript. All authors reviewed the manuscript.

Acknowledgements

The Guangzhou Biobank Cohort Study investigators included Guangzhou Twelfth People’s Hospital: Weisen Zhang, Min Cao, Tong Zhu, Bin Liu, and Caoqiang Jiang (Co-PI); The University of Hong Kong: C.M. Schooling, S.M. McGhee, G.M. Leung, R. Fielding, and Taihing Lam (Co-PI); The University of Birmingham: P. Adab, G. Neil Thomas, and Karkeung Cheng (Co-PI).

References

1. Stroke—1989. Recommendations on stroke prevention, diagnosis, and therapy. Report of the WHO Task Force on Stroke and other Cerebrovascular Disorders. Stroke 1989, 20(10):1407-1431.
2. Murray KN, Buggey HF, Denes A, Allan SM: Systemic immune activation shapes stroke outcome. Molecular and cellular neurosciences 2013, 53:14-25.
3. Welsh P, Barber M, Langhome P, Rumley A, Lowe GD, Stott DJ: Association of inflammatory and haemostatic biomarkers with poor outcome in acute ischaemic stroke. Cerebrovascular diseases 2009, 27(3):247-253.
4. Moskowitz MA, Lo EH, Iadecola C: The science of stroke: mechanisms in search of treatments. Neuron 2010, 67(2):181-198.
5. Sun W, Peacock A, Becker J, Phillips-Bute B, Laskowitz DT, James ML: Correlation of leukocytosis with early neurological deterioration following supratentorial intracerebral hemorrhage. Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia 2012, 19(8):1096-1100.
6. Parthasarathy S, Steinberg D, Witztum JL: The role of oxidized low-density lipoproteins in the pathogenesis of atherosclerosis. Annual review of medicine 1992, 43:219-225.
7. Kazmierski R, Gzik P, Ambrosius W, Ciesielska A, Moskal J, Kozubski W: Predictive value of white blood cell count on admission for in-hospital mortality in acute stroke patients. Clinical neurology and neurosurgery 2004, 107(1):38-43.
8. Algina A, Inan I: The role of radiologic, clinical and biochemical parameters in prediction of stroke mortality. Neurosciences 2019, 24(2):110-114.
9. Qu X, Shi J, Cao Y, Zhang M, Xu J: Prognostic Value of White Blood Cell Counts and C-reactive Protein in Acute Ischemic Stroke Patients After Intravenous Thrombolysis. Current neurovascular research 2018, 15(1):10-17.
10. Ho WM, Lin JR, Wang HH, Liou CW, Chang KC, Lee JD, Peng TY, Yang JT, Chang YJ, Chang CH et al: Prediction of in-hospital stroke mortality in critical care unit. SpringerPlus 2016, 5(1):1051.
11. Brown DW, Ford ES, Giles WH, Croft JB, Balluz LS, Mokdad AH: Associations between white blood cell count and risk for cerebrovascular disease mortality: NHANES II Mortality Study, 1976-1992. Annals of epidemiology 2004, 14(6):425-430.
12. Margolis KL, Manson JE, Greenland P, Rodabough RJ, Bray PF, Safford M, Grimm RH, Jr., Howard BV, Assaf AR, Prentice R et al: Leukocyte count as a predictor of cardiovascular events and mortality in postmenopausal women: the Women’s Health Initiative Observational Study. Archives of internal medicine 2005, 165(5):500-508.
13. Kabagambe EK, Judd SE, Howard VJ, Zakai NA, Jenny NS, Hsieh M, Warnock DG, Cushman M: Inflammation biomarkers and risk of all-cause mortality in the Reasons for Geographic And Racial Differences in Stroke cohort. American journal of epidemiology 2011, 174(3):284-292.
14. Wang T, Jiang CQ, Xu L, Zhang WS, Zhu F, Jin YL, Thomas GN, Cheng KK, Lam TH: White blood cell count and all-cause and cause-specific mortality in the Guangzhou biobank cohort study. BMC public health 2018, 18(1):1232.
15. Huh JY, Ross GW, Chen R, Abbott RD, Bell C, Willcox B, Launer L, Petrovitch H, Kaya B, Masaki K: Total and differential white blood cell counts in late life predict 8-year incident stroke: the Honolulu Heart Program. Journal of the American Geriatrics Society 2015, 63(3):439-446.
16. Park JK, Kim HJ, Chang SJ, Koh SB, Koh SY: Risk factors for hemorrhagic stroke in Wonju, Korea. Yonsei medical journal 1998, 39(3):229-235.
17. Lee CD, Folsom AR, Nieto FJ, Chambliss LE, Shahar E, Wolfe DA: White blood cell count and incidence of coronary heart disease and ischemic stroke and mortality from cardiovascular disease in African-American and White men and women: atherosclerosis risk in communities study. American journal of epidemiology 2001, 154(5):758-764.
18. Koren-Morag N, Tanne D, Goldboult U: White blood cell count and the incidence of ischemic stroke in coronary heart disease patients. The American journal of medicine 2005, 118(9):1004-1009.
19. Zia E, Melander O, Bjorkbacka H, Hedblad B, Engstrom G: Total and differential leucocyte counts in relation to incidence of stroke subtypes and mortality: a prospective cohort study. Journal of internal medicine 2012, 272(3):298-304.
20. Wu TH, Chien KL, Lin HJ, Hsu HC, Su TC, Chen MF, Lee YT: Total white blood cell count or neutrophil count predict ischemic stroke events among adult Taiwanese: report from a community-based cohort study. BMC neurology 2013, 13.7.
21. Gillum RF, Ingram DD, Makuc DM: White blood cell count and stroke incidence and death. The NHANES I epidemiologic follow-up study. American journal of epidemiology 1994, 139(9):894-902.
22. Froyshov HM, Bjomerem A, Engstad T, Halvorsen DS: Elevated inflammatory markers predict mortality in long-term ischemic stroke-survivors: a population-based prospective study. Aging clinical and experimental research 2017, 29(3):379-385.
23. Ohira T, Shahar E, Chambliss LE, Rosamond WD, Mosley TH, Jr., Folsom AR: Risk factors for ischemic stroke subtypes: the Atherosclerosis Risk in Communities study. Stroke 2006, 37(10):2493-2498.
24. Wang L, Song Q, Wang C, Wu S, Deng L, Li Y, Zheng L, Liu M: Neutrophil to lymphocyte ratio predicts poor outcomes after acute ischemic stroke: A cohort study and systematic review. *Journal of the neurological sciences* 2019, 406:116445.

25. Freeburn JC, Wallace JM, Strain JJ, Sinnamon DG, Craig BM, Johnson D, Gilmore WS: Monocyte tissue factor-like activity in post myocardial infarction patients. *British journal of haematology* 1998, 102(2):605-608.

26. Ye JK, Zhang JT, Kong Y, Xu T, Zou TT, Zhang YH, Zhang SY: [Relationship between white blood cell count, neutrophil ratio and erythrocyte sedimentation rate and short clinical outcomes among patients with acute ischemic stroke at hospital admission]. Zhonghua liu xing bing xue za zhi = Zhonghua liuxingbingxue zazhi 2012, 32(9):956-960.

27. Walsh KB, Sekar P, Langefeld CD, Moomaj CJ, Elkind MS, Boehme AK, James ML, Osborne J, Sheth KN, Woo D et al: Monocyte Count and 30-Day Case Fatality In Intracerebral Hemorrhage. *Stroke* 2015, 46(8):2302-2304.

28. Iso H, Cui R, Date C, Kikuchi S, Tamakoshi A, Group JS: C-Reactive protein levels and risk of mortality from cardiovascular disease in Japanese: the JACC Study. *Atherosclerosis* 2009, 207(1):291-297.

29. Arevalo-Lorido JC, Carretero-Gomez J, Fernandez-Recio JM, Alvarez-Oliva A, Gutierrez-Montano C, Najarro-Diez F, Martin-Sanchez MJ: Lowering C-Reactive protein with statins after an ischemic stroke avoids mortality and readmissions. A prospective cohort study. *Annals of medicine* 2015, 47(3):226-232.

30. Bakhshayesh-Eghbali B, Roudbari SA, Basir Jafari S, Nabizadeh SP, Naderi-Asrami N, Sohrabnejad R: Ability of serum C-Reactive protein and white blood cell count in predicting acute ischemic stroke. *A short-term follow-up study*. *Caspianna journal of internal medicine* 2016, 7(3):206-210.

31. Lao XQ, Neil Thomas G, Jiang C, Zhang W, Adap P, Lam TH, Cheng KK: White blood cell count and the metabolic syndrome in older Chinese: the Guangzhou Biobank Cohort Study. *Atherosclerosis* 2008, 201(2):418-424.

32. Phillips AC, Jiang CQ, Thomas GN, Lin JM, Yue XJ, Cheng KK, Jin YL, Zhang WS, Lam TH: White blood cell subsets are associated with carotid intima-media thickness and pulse wave velocity in an older Chinese population: the Guangzhou Biobank Cohort Study. *Journal of human hypertension* 2012, 26(8):485-492.

33. Jiang C, Thomas GN, Lam TH, Schooling CM, Zhang W, Lao X, Adap P, Liu B, Leung GM, Cheng KK: Cohort profile: The Guangzhou Biobank Cohort Study, a Guangzhou-Hong Kong-Birmingham collaboration. *International journal of epidemiology* 2006, 35(4):844-852.

34. Deng HB, Macfarlane DJ, Thomas GN, Lao XQ, Jiang CQ, Cheng KK, Lam TH: Reliability and validity of the IPAQ-Chinese: the Guangzhou Biobank Cohort study. *Medicine and science in sports and exercise* 2008, 40(2):303-307.

35. Chen C, Lu FC, Department of Disease Control Ministry of Health PRC: The guidelines for prevention and control of overweight and obesity in Chinese adults. *Biomedical and environmental sciences : BES* 2004, 17 Suppl 1-36.

36. Furlan JC, Vergouwen MD, Fang J, Silver FL: White blood cell count is an independent predictor of outcomes after acute ischaemic stroke. *European journal of neurology* 2014, 21(2):215-222.

37. Nayak AR, Kashyap RS, Kabra D, Deoras P, Purohit HJ, Taori GM, Daginawala HF: Evaluation of routinely performed hematological and biochemical parameters for the prognosis of acute ischemic stroke patients. *Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology* 2011, 32(5):855-860.

38. Kammersgaard LP, Jorgensen HS, Nakayama H, Reith J, Raaschou HO, Olsen TS: Leukocytosis in acute stroke: relation to initial stroke severity, infarct size, and outcome: the Copenhagen Stroke Study. *Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association* 1999, 8(4):259-263.

39. Kerr R, Stirling D, Ludlam CA: Interleukin 6 and haemostasis. *British journal of haematology* 2001, 115(1):3-12.

40. Denes A, Ferenczi S, Kovacs KJ: Systemic inflammatory challenges compromise survival after experimental stroke via augmenting brain inflammation, blood-brain barrier damage and brain oedema independently of infarct size. *Journal of neuroinflammation* 2011, 8:164.

41. Li T, Wu XJ, Chen XM, Wang SB, Liu KD, Xing YQ: Ankle-brachial index and brachial-ankle pulse wave velocity are risk factors for ischemic stroke in patients with Type 2 diabetes. *Neural regeneration research* 2017, 12(11):1853-1859.

42. Kim J, Song TJ, Song D, Lee JK, Kim EH, Lee HS, Nam CM, Nam HS, Kim YD, Heo JH: Brachial-ankle pulse wave velocity is a strong predictor for mortality in patients with acute stroke. *Hypertension* 2014, 64(2):240-246.

43. Proctor MJ, McMillan DC, Horgan PG, Fletcher CD, Talwar D, Morrison DS: Systemic inflammation predicts all-cause mortality: a glasgow inflammation outcome study. *Plos one* 2015, 10(3):e0116206.

44. Jickling GC, Liu D, Ander BP, Stamova B, Zhan X, Sharp FR: Targeting neutrophils in ischemic stroke: translational insights from experimental studies. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism* 2015, 35(6):888-901.

45. Song SY, Zhao XX, Rajah G, Hua C, Kang RJ, Han YP, Ding YC, Meng R: Clinical Significance of Baseline Neutrophil-to-Lymphocyte Ratio in Patients With Ischemic Stroke or Hemorrhagic Stroke: An Updated Meta-Analysis. *Frontiers in neurology* 2019, 10:1032.

46. Qin J, Li Z, Gong G, Li H, Chen L, Song B, Liu X, Shi C, Yang J, Yang T et al: Early Increased neutrophil-to-lymphocyte ratio is associated with poor 3-month outcomes in spontaneous intracerebral hemorrhage. *Plos one* 2019, 14(2):e0211833.

47. Giede-Jeppe A, Reichl J, Sprugel MJ, Lucking H, Hoelter F, Eyupoglu IU, Kuramatsu JB, Huttner HB, Gerner ST: Neutrophil-to-lymphocyte ratio as an independent predictor for unfavorable functional outcome in aneurysmal subarachnoid hemorrhage. *Journal of neurosurgery* 2019, 132(2):400-407.

48. Lattanzi S, Cagnetti C, Rinaldi C, Angelocola S, Provinciali L, Silvestrini M: Neutrophil-to-lymphocyte ratio improves outcome prediction of acute intracerebral hemorrhage. *Journal of the neurological sciences* 2018, 387:98-102.

49. Ye Z, Ai X, Fang F, Hu X, Faramand A, You C: The use of neutrophil to lymphocyte ratio as a predictor for clinical outcomes in spontaneous intracerebral hemorrhage. *Oncotarget* 2017, 8(52):90380-90389.
50. Tao C, Hu X, Wang J, Ma J, Li H, You C: Admission neutrophil count and neutrophil to lymphocyte ratio predict 90-day outcome in intracerebral hemorrhage. Biomarkers in medicine 2017, 11(1):33-42.

51. Sun Y, You S, Zhong C, Huang Z, Hu L, Zhang X, Shi J, Cao Y, Liu CF: Neutrophil to lymphocyte ratio and the hematoma volume and stroke severity in acute intracerebral hemorrhage patients. The American journal of emergency medicine 2017, 35(3):429-433.

52. Wang F, Hu S, Ding Y, Ju X, Wang L, Lu Q, Wu X: Neutrophil-to-Lymphocyte Ratio and 30-Day Mortality in Patients with Acute Intracerebral Hemorrhage. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association 2016, 25(1):182-187.

53. Zhang F, Ren Y, Fu W, Yang Z, Wen D, Hu X, Tao C, Li X, You C, Xin T et al: Predictive Accuracy of Neutrophil-to-Lymphocyte Ratio on Long-Term Outcome in Patients with Spontaneous Intracerebral Hemorrhage. World neurosurgery 2019, 125:e651-e657.

54. Chamberlain AC, Turner FM, Williams EK: The evaluation of white-cell counting in radiation protection. The British journal of radiology 1952, 25(292):169-176.

Tables
## Table 1 Baseline characteristics by WBC count quartiles of participants in the GBCS, 2003-2017 (n=27811)

| Characteristics          | Quartiles of WBC count (*10^9/L) | \(P\) value trend |
|--------------------------|----------------------------------|-------------------|
|                          | 1\(^{\text{st}}\) quartile (<5.3) | 2\(^{\text{nd}}\) quartile (5.3-6.1) | 3\(^{\text{rd}}\) quartile (6.2-7.2) | 4\(^{\text{th}}\) quartile (>7.2) |
| Number, n                | 6946                            | 6912              | 7093                  | 6860                  |
| Sex, male (%)            | 1.1468(21.1)                    | 1.1767(25.6)      | 2.2004(28.3)          | 2.2392(34.9)          |
| Age (years)              | 61.1±7.1                        | 61.8±7.2          | 62.3±7.0              | 62.9±7.0              |
| Education (%)            | <0.001                          | <0.001            | <0.001                | <0.001                |
| Primary or below         | 2536 (36.5)                     | 2861 (41.4)       | 3177 (44.8)           | 3406 (49.7)           |
| Middle school            | 3685 (53.1)                     | 3405 (49.3)       | 3352 (47.3)           | 2932 (42.7)           |
| College or above         | 725 (10.4)                      | 646 (9.3)         | 564 (8.0)             | 522 (7.6)             |
| Occupation               | <0.001                          | <0.001            | <0.001                | <0.001                |
| Manual                   | 3277 (47.2)                     | 3346 (48.4)       | 3551 (50.1)           | 3565 (52.0)           |
| Non-manual               | 2267 (32.6)                     | 2262 (32.7)       | 2294 (32.3)           | 2130 (31.0)           |
| Others                   | 1402 (22.2)                     | 1304 (18.9)       | 1248 (17.6)           | 1165 (17.0)           |
| Smoking habit, n (%)     | <0.001                          | <0.001            | <0.001                | <0.001                |
| Never                    | 6086(87.6)                      | 5822(84.2)        | 5708(80.5)            | 4909(71.6)            |
| Former                   | 530(7.6)                        | 596(8.6)          | 682(9.6)              | 714(10.4)             |
| Current                  | 330(4.8)                        | 494(7.2)          | 703(9.9)              | 1237(18.0)            |
| Alcohol consumption, n (%)| <0.001                          | <0.001            | <0.001                | <0.001                |
| Never                    | 5016(72.2)                      | 4835(70.0)        | 4965(70.0)            | 4725(68.9)            |
| Former                   | 119(1.7)                        | 150(2.2)          | 169(2.4)              | 203(3.0)              |
| Current                  | 1811(26.1)                      | 1927(27.8)        | 1959(27.6)            | 1932(28.1)            |
| Physical activity, IPAQ, n (%) | <0.001                      | <0.001            | <0.001                | <0.001                |
| Inactive                 | 649(9.3)                        | 505(7.3)          | 560(7.9)              | 541(7.9)              |
| Minimally active         | 2844(41.0)                      | 2771(40.1)        | 2855(40.2)            | 2876(41.9)            |
| HEPA active              | 3453(49.7)                      | 3636(52.6)        | 3678(51.9)            | 3443(50.2)            |
| Body mass index, kg/m²   | <0.001                          | <0.001            | <0.001                | <0.001                |
| <18.5                    | 562(8.1)                        | 295(4.3)          | 199(2.8)              | 190(2.8)              |
| 18.5-23.9                | 4119(59.3)                      | 3608(52.2)        | 3339(47.1)            | 2882(42.0)            |
| 24-27.9                  | 1909(27.5)                      | 2429(35.1)        | 2734(38.5)            | 2785(40.6)            |
| ≥28                      | 356(5.1)                        | 580(8.4)          | 821(11.6)             | 1003(14.6)            |
| Self-rated health, n (%) | <0.001                          | <0.001            | <0.001                | <0.001                |
| (good/very good)         | 5724(82.4)                      | 5793(83.8)        | 5899(83.2)            | 5561(81.1)            |
| Hypertension, n (%)      | <0.001                          | <0.001            | <0.001                | <0.001                |
| Diabetes, n (%)          | 522(7.5)                        | 751(10.9)         | 997(14.1)             | 1359(19.8)            |
| Dyslipidaemia, n (%)     | 5517(79.4)                      | 5694(82.4)        | 5985(84.4)            | 5828(85.0)            |
| Cancer, n (%)            | 180(2.6)                        | 137(2.0)          | 122(1.7)              | 100(1.5)              |
| GU disease, n (%)        | 2035(29.3)                      | 1873(27.1)        | 1853(26.1)            | 1644(24.0)            |
| Chest disease, n (%)     | 1060(15.3)                      | 1076(15.6)        | 1039(14.6)            | 1038(15.1)            |
| Neutrophils, *10⁹/L     | 2.6±0.76                        | 3.3±0.47          | 4.0±0.95              | 5.4±1.24              |
| Lymphocytes, *10⁹/L     | 1.7±0.36                        | 2.0±0.41          | 2.2±0.48              | 2.6±0.67              |
| Platelets, *10⁹/L       | 203.6±51.3                      | 221.6±57.7        | 233.9±55.7            | 250.4±65.8            |
| CRP, mg/L               | 2.8±2.4                         | 3.1±2.5           | 3.6±2.8               | 4.2±3.2               |
Hypertension: systolic blood pressure, ≥140 mmHg, or diastolic blood pressure, ≤90 mmHg, or medication or diagnosis; diabetes: fasting blood glucose ≥7 or medication or diagnosis; dyslipidaemia: total cholesterol ≥5.2 mmol/L, or triglyceride ≥1.7 mmol/L, or low density lipoprotein ≥3.4 mmol/L, or high density lipoprotein <1.0 mmol/L, or medication or diagnosis; WBC: white blood cell; CRP: C-reactive protein; GU: genitourinary disease (including nephropathy, prostatic disease, gynaecologic diseases); chest disease: including chronic obstructive pulmonary disease, chronic bronchitis, emphysema, asthma, tuberculosis, pneumonia.

Table 2 Association between leucocytes and stroke mortality in GBCS, 2003-2017 (n=27811)
| Quartile | WBC (*10^9/L) | NEU (*10^9/L) | P value trend | LYM (*10^9/L) |
|---------|---------------|---------------|---------------|---------------|
| 1st     | 82196         | 77783         |               | 80857         |
| 2nd     | 81955         | 79448         |               | 83038         |
| 3rd     | 82196         | 77783         |               | 80857         |
| 4th     | 82196         | 77783         |               | 80857         |

| Quartile | WBC (*10^9/L) | NEU (*10^9/L) | P value trend | LYM (*10^9/L) |
|---------|---------------|---------------|---------------|---------------|
| 1st     | 82196         | 77783         |               | 80857         |
| 2nd     | 81955         | 79448         |               | 83038         |
| 3rd     | 82196         | 77783         |               | 80857         |
| 4th     | 82196         | 77783         |               | 80857         |

**Table 3** Association between leucocytes within the normal range (4~10^9/L) and stroke mortality in GBCS from 2003-2017 (n=24,082)
| WBC (*10^9/L), n=24082 | P value | NEU (*10^9/L), n=23968 | P value |
|------------------------|---------|-------------------------|---------|
| 1st quartile           | 2nd quartile | 3rd quartile | 4th quartile | trend | 1st quartile | 2nd quartile | 3rd quartile | 4th quartile | trend |
| Person years           | 64170   | 74055                   | 75331   | 64985   | P         |
| per 10^5 person-years  | 99.7    | 114.8                   | 160.6   | 212.4   | value     |
| No. deaths             | 64      | 85                      | 121     | 138     | trend     |
| mHR (95%CI)*           | Ref. 1.01 (0.72-1.40) | 1.33 (0.97-1.82) | 1.56 (1.13-2.14) | 0.001 | Ref. 1.05 (0.75-1.48) | 1.17 (0.84-1.64) | 1.64 (1.19-2.26) | <0.001 |
| P value                | 0.97    | 0.08                    | 0.007   | 0.76    | 0.35      | 0.003    |
| faHR (95%CI)**         | Ref. 1.03 (0.66-1.60) | 1.38 (0.90-2.10) | 1.57 (1.02-2.42) | 0.012 | Ref. 0.97 (0.61-1.54) | 1.35 (0.87-2.09) | 1.55 (1.00-2.41) | 0.009 |
| P value                | 0.91    | 0.14                    | 0.04    | 0.88    | 0.19      | 0.05     |

| Total stroke           | 64170   | 74055                   | 75331   | 64985   | 66162 | 76172 | 71150 | 67682 |
| No. deaths             | 64      | 85                      | 121     | 138     | 56     | 89     | 101   | 160   |
| mHR (95%CI)*           | Ref. 1.01 (0.72-1.40) | 1.33 (0.97-1.82) | 1.56 (1.13-2.14) | 0.001 | Ref. 1.05 (0.75-1.48) | 1.17 (0.84-1.64) | 1.64 (1.19-2.26) | <0.001 |
| P value                | 0.97    | 0.08                    | 0.007   | 0.76    | 0.35      | 0.003    |
| faHR (95%CI)**         | Ref. 1.03 (0.66-1.60) | 1.38 (0.90-2.10) | 1.57 (1.02-2.42) | 0.012 | Ref. 0.97 (0.61-1.54) | 1.35 (0.87-2.09) | 1.55 (1.00-2.41) | 0.009 |
| P value                | 0.91    | 0.14                    | 0.04    | 0.88    | 0.19      | 0.05     |

| Ischaemic stroke       | 64170   | 74055                   | 75331   | 64985   | 66162 | 76172 | 71150 | 67682 |
| No. deaths             | 64      | 85                      | 121     | 138     | 56     | 89     | 101   | 160   |
| mHR (95%CI)*           | Ref. 1.01 (0.72-1.40) | 1.33 (0.97-1.82) | 1.56 (1.13-2.14) | 0.001 | Ref. 1.05 (0.75-1.48) | 1.17 (0.84-1.64) | 1.64 (1.19-2.26) | <0.001 |
| P value                | 0.97    | 0.08                    | 0.007   | 0.76    | 0.35      | 0.003    |
| faHR (95%CI)**         | Ref. 1.03 (0.66-1.60) | 1.38 (0.90-2.10) | 1.57 (1.02-2.42) | 0.012 | Ref. 0.97 (0.61-1.54) | 1.35 (0.87-2.09) | 1.55 (1.00-2.41) | 0.009 |
| P value                | 0.91    | 0.14                    | 0.04    | 0.88    | 0.19      | 0.05     |

| Haemorrhagic stroke    | 64170   | 74055                   | 75331   | 64985   | 66162 | 76172 | 71150 | 67682 |
| No. deaths             | 64      | 85                      | 121     | 138     | 56     | 89     | 101   | 160   |
| mHR (95%CI)*           | Ref. 1.01 (0.72-1.40) | 1.33 (0.97-1.82) | 1.56 (1.13-2.14) | 0.001 | Ref. 1.05 (0.75-1.48) | 1.17 (0.84-1.64) | 1.64 (1.19-2.26) | <0.001 |
| P value                | 0.97    | 0.08                    | 0.007   | 0.76    | 0.35      | 0.003    |
| faHR (95%CI)**         | Ref. 1.03 (0.66-1.60) | 1.38 (0.90-2.10) | 1.57 (1.02-2.42) | 0.012 | Ref. 0.97 (0.61-1.54) | 1.35 (0.87-2.09) | 1.55 (1.00-2.41) | 0.009 |
| P value                | 0.91    | 0.14                    | 0.04    | 0.88    | 0.19      | 0.05     |

Ref: reference; mHR: multivariate adjusted hazard ratio; faHR: further adjusted hazard ratio; CI: confidence interval. C: P<0.001, a: P<0.01, b: P<0.05. #: Adjusted for sex, age, education, occupation, diabetes, hypertension, dyslipidaemia, smoking habit, alcohol consumption, physical activity, body mass index, self-rated health, cancer, genitourinary disease (including nephropathy, prostatic disease, gynaecologic diseases), chest disease (including chronic obstructive pulmonary disease, chronic bronchitis, emphysema, asthma, tuberculosis, pneumonia) and platelet count. WBC analysis on further CRP adjustment was performed on 10041 participants. Neutrophil analysis excluded participants with stroke and CVD and with a NEU count in the top 1% and bottom 1% and was performed with further CRP adjustment in 9946 participants.

Table 4 Association between hs-CRP and stroke mortality in the GBCS, 2003-2017 (n=11601)
|                | Total stroke | Ischaemic stroke | Haemorrhagic stroke |
|----------------|--------------|------------------|--------------------|
|                | WBC ($10^9/L$) | 1<sup>st</sup> quartile | 2<sup>nd</sup> quartile | 3<sup>rd</sup> quartile | 4<sup>th</sup> quartile | P value trend | 1<sup>st</sup> quartile | 2<sup>nd</sup> quartile | 3<sup>rd</sup> quartile | 4<sup>th</sup> quartile | P value trend |
| **Overall**    |              |                  |                    |                       |                    |             |          |                  |                    |                       |             |             |             |
| Person years   | 34882        | 3512            |                    |                       |                    |             |          | 35665            | 35765            |                    |             |             |             |
| per 10<sup>5</sup> years | 177.8       | 186.2           |                    |                       |                    |             |          | 243.9           | 86.7             |                    |             |             |             |
| No. deaths     | 62           | 67              | 87                | 30                     | 32                 | 30          | 39       | 20               | 25               | 20                 | 29          |
| **cHR** (95%CI) | Ref. 1.02    | 0.99            | 1.31              | 0.12                   | Ref. 0.98          | 0.90        | 1.19     | Ref. 1.17        | 0.93             | 1.38               |
|                | (0.72-1.44)  | (0.70-1.40)     | (0.94-1.81)        |                        | (0.60-1.62)        | (0.55-1.50) | (0.74-1.92) | (0.65-2.11)      | (0.50-1.73)      | (0.78-2.44)         |
| **P value**    | 0.92         | 0.96            | 0.11              | 0.95                   | 0.70              | 0.48       | 0.60     | 0.82             | 0.27             |
| **aHR<sup>a</sup>** (95% CI) | Ref. 0.93     | 0.85            | 1.04              | 0.87                   | Ref. 0.90          | 0.78        | 0.92     | Ref. 1.07        | 0.81             | 1.16               |
|                | (0.66-1.32)  | (0.61-1.21)     | (0.74-1.47)        |                        | (0.54-1.48)        | (0.47-1.31) | (0.56-1.53) | (0.59-1.93)      | (0.43-1.52)      | (0.64-2.11)         |
| **P value**    | 0.69         | 0.38            | 0.81              | 0.66                   | 0.36              | 0.76       | 0.84     | 0.51             | 0.62             |

Ref: reference; cHR: crude hazard ratio; aHR: adjusted hazard ratio; CI: confidence interval. C P<0.001, b P<0.01, *P<0.05. Adjusted for sex, age, education, occupation, diabetes, hypertension, dyslipidaemia, smoking habit, alcohol consumption, physical activity, body mass index, self-rated health, cancer, genitourinary disease (including nephropathy, prostatic disease, gynaecologic diseases), chest disease (including chronic obstructive pulmonary disease, chronic bronchitis, emphysema, asthma, tuberculosis, pneumonia), WBC count and platelet count.

**Table 5** Association between leucocyte changes and stroke mortality in GBCS, 2003-2012 (n=16296)
|                      | Total stroke | Ischaemic stroke | Haemorrhagic stroke |
|----------------------|--------------|------------------|--------------------|
| **Mode1**            |              |                  |                    |
|                      | Loss (<10%)  | Stable (<10%-10%)| Gain (>10%)        |
|                      | Loss (<10%)  | Stable (<10%-10%)| Gain (>10%)        |
|                      | Loss (<10%)  | Stable (<10%-10%)| Gain (>10%)        |
|                      | Loss (<10%)  | Stable (<10%-10%)| Gain (>10%)        |
|                      | Loss (<10%)  | Stable (<10%-10%)| Gain (>10%)        |
| **WBC change**       |              |                  |                    |
| Person years         | 33933        | 57901            | 36426              |
| per 10^5 person-years| 135.6        | 134.7            | 183.9              |
|                      | 73.9         | 71.0             | 77.3               |
|                      | 41.5         | 41.7             | 63.6               |
| No. deaths           | 46           | 78               | 67                 |
|                      | 25           | 41               | 28                 |
|                      | 14           | 24               | 23                 |
| cHR (95%CI)          | 1.01 (0.70-1.45) | Ref.             | 1.36 (0.98-1.89) |
|                      | 1.05 (0.64-1.73) | Ref.             | 1.08 (0.67-1.74) |
|                      | 0.99 (0.51-1.91) | Ref.             | 1.54 (0.87-2.73) |
| P value              | 0.96         | 0.07             | 0.85               |
|                      | 0.76         | 0.97             | 0.97               |
| aHR (95% CI)         | 0.93 (0.64-1.34) | Ref.             | 1.35 (0.97-1.88) |
|                      | 0.92 (0.56-1.52) | Ref.             | 1.06 (0.66-1.72) |
|                      | 0.94 (0.48-1.82) | Ref.             | 1.48 (0.83-2.63) |
| P value              | 0.70         | 0.08             | 0.75               |
|                      | 0.80         | 0.85             | 0.18               |
| **NEU change**       |              |                  |                    |
| Person years         | 43239        | 43221            | 41800              |
| per 10^5 person-years| 115.6        | 150.4            | 181.8              |
|                      | 64.9         | 76.6             | 79.4               |
|                      | 32.5         | 46.5             | 65.1               |
| No. deaths           | 50           | 65               | 76                 |
|                      | 28           | 33               | 33                 |
|                      | 14           | 20               | 27                 |
| cHR (95%CI)          | 0.76 (0.53-1.10) | Ref.             | 1.21 (0.87-1.69) |
|                      | 0.85 (0.51-1.40) | Ref.             | 1.04 (0.64-1.68) |
|                      | 0.69 (0.35-1.36) | Ref.             | 1.41 (0.79-2.52) |
| P value              | 0.15         | 0.25             | 0.52               |
|                      | 0.89         | 0.28             | 0.24               |
| aHR (95% CI)         | 0.72 (0.49-1.04) | Ref.             | 1.18 (0.85-1.65) |
|                      | 0.75 (0.45-1.24) | Ref.             | 1.00 (0.61-1.62) |
|                      | 0.69 (0.35-1.37) | Ref.             | 1.38 (0.77-2.46) |
| P value              | 0.08         | 0.33             | 0.26               |
|                      | 0.99         | 0.29             | 0.28               |
| **Mode2**            | Loss (<25%)  | Stable (-25%-25%)| Gain (>25%)        |
|                      | Loss (<25%)  | Stable (-25%-25%)| Gain (>25%)        |
|                      | Loss (<25%)  | Stable (-25%-25%)| Gain (>25%)        |
|                      | Loss (<25%)  | Stable (-25%-25%)| Gain (>25%)        |
|                      | Loss (<25%)  | Stable (-25%-25%)| Gain (>25%)        |
| **WBC change**       |              |                  |                    |
| Person years         | 7992         | 107611           | 12657              |
| per 10^5 person-years| 162.7        | 139.4            | 221.2              |
|                      | 112.9        | 67.1             | 103.5              |
|                      | 46.6         | 46.6             | 63.9               |
| No. deaths           | 13           | 150              | 28                 |
|                      | 9            | 72               | 13                 |
|                      | 3            | 50               | 8                  |
| cHR (95%CI)          | 1.18 (0.67-2.08) | Ref.             | 1.58 (1.06-1.37) |
|                      | 1.72 (0.86-3.43) | Ref.             | 1.53 (0.85-2.76) |
|                      | 0.80 (0.25-2.57) | Ref.             | 1.38 (0.65-2.91) |
| P value              | 0.57         | 0.03             | 0.13               |
|                      | 0.16         | 0.71             | 0.40               |
| aHR (95% CI)         | 1.05 (0.59-1.85) | Ref.             | 1.60 (1.07-2.40) |
|                      | 1.48 (0.74-2.98) | Ref.             | 1.58 (0.87-2.87) |
|                      | 0.77 (0.24-2.46) | Ref.             | 1.37 (0.65-2.92) |
| P value              | 0.86         | 0.02             | 0.27               |
|                      | 0.13         | 0.65             | 0.41               |
| **NEU change**       |              |                  |                    |
| Person years         | 17019        | 89795            | 21445              |
| per 10^5 person-years| 129.3        | 140.3            | 200.5              |
|                      | 94.2         | 63.7             | 98.5               |
|                      | 29.5         | 48.1             | 61.2               |
| No. deaths           | 22           | 126              | 43                 |
|                      | 16           | 57               | 21                 |
|                      | 5            | 43               | 13                 |
| cHR (95%CI)          | 0.92 (0.59-1.45) | Ref.             | 1.43 (1.02-2.03) |
|                      | 1.49 (0.86-2.60) | Ref.             | 1.54 (0.94-2.55) |
|                      | 0.61 (0.24-1.53) | Ref.             | 1.29 (0.69-2.39) |
| P value | 0.72 | 0.04 | 0.16 | 0.09 | 0.29 | 0.43 |
|---------|------|------|------|------|------|------|
| aHR^a (95% CI) | 0.88 (0.56-1.38) | Ref. | 1.45 (1.02-2.05)^a | 1.37 (0.79-2.40) | Ref. | 1.59 (0.96-2.64) | 0.61 (0.24-1.54) | Ref. | 1.25 (0.67-2.34) |

| P value | 0.57 | 0.04 | 0.27 | 0.07 | 0.30 | 0.49 |

Ref: reference; cHR: crude hazard ratio; aHR: adjusted hazard ratio; CI: confidence interval; C P<0.001, b P<0.01, a P<0.05. *: Adjusted for sex, age, education, occupation, diabetes, hypertension, dyslipidaemia, smoking habit, alcohol consumption, physical activity, body mass index, self-rated health, cancer, genitourinary disease (including nephropathy, prostatic disease, gynaecologic diseases), chest disease (including chronic obstructive pulmonary disease, chronic bronchitis, emphysema, asthma, tuberculosis, pneumonia) and platelet count.