The population characteristics of the main leukocyte subsets and their association with chronic diseases in a community-dwelling population: a cross-sectional study

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Abstract

Aim: To analyse the characteristics of the main leukocyte subsets and elucidate their distributions amongst the natural population. We wanted to determine whether leukocyte subsets are potential biomarkers to evaluate the risk of common chronic diseases. Background: The peripheral blood leukocyte count is a routine exam performed to detect pathogen infections. Recently, subsets of white blood cells and their homeostasis have shown strong associations with some chronic diseases. Therefore, studies aiming to discover whether the distribution of leukocyte counts and its subsets are useful for predicting health conditions are worthwhile. Methods: This cross-sectional study analysed 10 564 residents from the basic public health service project of the Health Checkup Program performed by the BaiYun Community Health Service Center. Data on demographic information, physical measurements, medical history, and routine blood examination parameters were collected using questionnaires and health check-ups. Restricted cubic spline incorporated into logistic regression analysis was performed to evaluate the association between subsets of leukocytes and chronic common diseases. Findings: The counts of leukocytes and their subsets in males were higher than those in females amongst all age groups, yet the percentages of lymphocytes and neutrophils did not present sex-specific differences. A low lymphocyte count and percentage were associated with old age. The neutrophil-to-lymphocyte ratio (NLR) and monocyte-to-lymphocyte ratio (MLR) are proxy markers for systemic inflammation (Pinato et al., 2012). Furthermore, leukocytes have been established to correlate with high blood pressure (Rodriguez-Iturbe et al., 2017). Given the strong association of leukocytes with health conditions, mechanistic studies on the relationship between them have been gradually reported. Leukocyte homeostasis and the ratio of each subset of cells or component modulation are complex. Research has suggested that one neutrophil subset (polymorphonuclear myeloid-derived suppressor cells) exerts inhibitory effects on lymphocytes, specifically the inhibition of lymphocyte proliferation (Lang et al., 2018). The ratio of neutrophils to lymphocytes positively correlates with age in the healthy population (Li et al., 2015). The lymphocyte number, neutrophil count, and platelet count were found to have significantly positive linear correlations with obesity, which is a confirmed risk factor for some chronic diseases (Furuncuoglu et al., 2016). As many factors contribute to the fluctuation of the leukocyte count, a systematic approach is necessary to understand the relationship between leukocyte subsets and chronic diseases.

Introduction

The peripheral blood leukocyte count has been considered to play important roles in the cellular-mediated inflammatory response. Recent studies have provided extensive information on the robust relationship of leukocytes, especially their subsets of cells, with chronic diseases such as stroke, diabetes mellitus, hypertension (Lee et al., 2017; Demirdal & Sen, 2018). Peripheral lymphocytes, neutrophils, monocytes, eosinophils, and basophils are the main subsets of white blood cells. The neutrophil-to-lymphocyte ratio (NLR) and monocyte-to-lymphocyte ratio (MLR) are proxy markers for systemic inflammation (Pinato et al., 2012). Some studies discovered correlations between many inflammation-associated diseases such as intracranial atherosclerosis (Nam et al., 2018), type 2 diabetes (Mertoglu & Gunay, 2017), and hypertension (Huang et al., 2019), and the NLR or MLR. Furthermore, leukocytes have been established to correlate with high blood pressure (Rodriguez-Iturbe et al., 2017). Given the strong association of leukocytes with health conditions, mechanistic studies on the relationship between them have been gradually reported. Leukocyte homeostasis and the ratio of each subset of cells or component modulation are complex. Research has suggested that one neutrophil subset (polymorphonuclear myeloid-derived suppressor cells) exerts inhibitory effects on lymphocytes, specifically the inhibition of lymphocyte proliferation (Lang et al., 2018). The ratio of neutrophils to lymphocytes positively correlates with age in the healthy population (Li et al., 2015). The lymphocyte number, neutrophil count, and platelet count were found to have significantly positive linear correlations with obesity, which is a confirmed risk factor for some chronic diseases (Furuncuoglu et al., 2016). As many factors contribute to the fluctuation of the leukocyte count, a systematic approach is necessary to understand the relationship between leukocyte subsets and chronic diseases.
Hypertension was defined as systolic blood pressure $\geq$ 140 mmHg or diastolic blood pressure $\geq$ 90 mmHg, a previous diagnosis of hypertension, and the use of any antihypertensive drugs. Type 2 diabetes mellitus was defined as fasting blood glucose levels $\geq$ 7.0 mmol/L, a previous diagnosis of diabetes mellitus or the use of any hypoglycaemic drugs. Stoke includes ischaemic and haemorrhagic stroke subtypes and was distinguished according to the presenting symptoms, such as awakening with or experiencing the abrupt onset of focal neurological deficits and non-contrast head computed tomography imaging indicating haemorrhage or ischaemic change in the medical records.

In this study, chronic disease refers to the hypertension, type 2 diabetes mellitus, and stroke listed above.

### Statistical analysis
Continuous data are presented as the means ± standard deviations for quantitative variables, and categorical variables are presented as percentages. Differences in normal variables between groups were tested using Student’s $t$-test, and non-normal data were tested using the Mann–Whitney $U$ test. The chi-square test was applied to analyse categorical data. The main effects of cell counts and percentages were tested using the general linear model. The NLR and MLR values were divided into quartiles as 25%, 50%, and 75% of each marker, and the first quartile was used as a reference in the multivariable analysis. The potential of blood immune cell parameters to predict the risk of target chronic diseases was estimated using a logistic regression model. Restricted cubic spline regression was used to explore the potential dose–response relationship between chronic diseases and NLR, MLR.

Statistical analyses were performed using SPSS version 24.0 (IBM Corp.), and R version 4.0.3. Two-sided $P$-values <0.05 were regarded as indicating statistical significance.

## Results
### Characteristics of the participants
The majority of participants were female, accounting for 54.87% of the 10 564 subjects. Six-thousand and six-hundred one (6601) subjects were older people aged $\geq$ 60 years. Approximately 58.52% of participants were overweight (BMI $>$ 24 kg/m$^2$), and 7.05% of them were obese (BMI $>$ 30 kg/m$^2$). The trend for the mean BMI in different age groups was not the same between males and females. In the group aged less than 60 years, men had a higher BMI than women. However, the values were similar in the old population (Figure 1). The prevalence of hypertension, diabetes, and stroke was 47.34%, 16.25%, and 0.89%, respectively (Table 1).

### Association of peripheral blood white blood cell subsets with BMI
A significant difference in the types of peripheral blood immune cells was observed between males (6.36 ± 1.63 × 10$^9$) and females (5.83 ± 1.46 × 10$^9$) ($t = 17.407$, $P < 0.001$). The total white blood cell (WBC) count and principal component cell counts, such as neutrophil, lymphocyte, and monocyte counts, increased with the BMI. The percentages of neutrophils and monocytes decreased with increasing BMI, but the lymphocyte percentage was positively associated with BMI. More interestingly, lymphocyte counts were not different between females and males ($F = 0.336$, $P = 0.562$), and lymphocyte percentages were higher in females than in males after adjusting for the variables age and BMI in the general linear model ($F = 298.88$, $P < 0.001$). The NLR was lowest in the largest BMI group, regardless of sex (Figure 1).

### Correlation of peripheral blood white blood cell subsets with age
We observed that the white blood cell counts significantly decreased with age ($F = 96.45$, $P$ trend <0.001), but the trend was not significant in females ($F = 3.448$, $P$ trend <0.063).
counts and percentages of neutrophils and lymphocytes fluctuated amongst different age groups. The monocyte count and percentage in males were higher than those in females in all age groups. However, the age-associated trend was not linear. These NLR data were not characteristic of age or sex specificity (Figure 2).

**NLR and MLR in patients with hypertension, diabetes, or stroke**

We compared the NLR and MLR between subjects with and without chronic disease such as hypertension, diabetes, and stroke. The NLR was higher in both females and males in the hypertension, but was higher in the female group with diabetes. The MLR was also higher in hypertensive subjects than in those without this disease; however, the difference between the MLR values of the two groups was not large. Significant differences in all of these indexes were not observed between the people with or without stroke (Table 2).

**Utility of NLR and MLR as risk biomarkers for hypertension and diabetes**

The results from logistic regression models showed that the NLR and MLR were associated with chronic diseases such as hypertension and diabetes after adjustment for age, sex, and BMI. As shown in Table 3, an elevated NLR was associated with the risk of hypertension, and the risk for patients in the top quartile of NLR was 1.19-fold higher (95% CI 1.05, 1.35) than for patients in the lowest quartile, while a high MLR also showed a correlation with an increased risk of hypertension in the lowest quartile (OR = 1.15, 95% CI 1.03, 1.29 for the second quartile). The NLR in the fourth quartile was associated with a statistically significantly increased risk of diabetes compared with the first quartile (OR = 1.40, 95% CI 1.19, 1.66). No factors except for age were significantly associated with the risk of stroke. The does–response relationship between NLR, MLR and chronic diseases risk was analysed by restricted cubic spline model. The results showed NLR and MLR were associated with risk of hypertension ($P_{\text{nonlinearity}} = 0.0241$ for NLR, $P_{\text{nonlinearity}} = 0.0257$ for MLR, respectively.) There was no non-linearity significance dose–response relationship of NLR, MLR with diabetes and stroke (Figure 3).

**Discussion**

In the present study, we retrospectively analysed the distribution of peripheral blood white blood cell subsets in a community population. The whole blood parameters from 10,564 adults showed that WBC counts were higher in males than in females ($6.36 \pm 1.63 \times 10^9$ in males versus $5.83 \pm 1.46 \times 10^9$ in females). No significant difference in the white blood cell count was observed between sexes and the white blood cell count was slightly higher in women amongst the adult healthy population in previous studies (Elderdery & Alshaiban, 2017; Fondoh et al., 2020). The reasons why our results were inconsistent with previous reports were potentially attributed to the subjects recruited in this study. All participants in our study were older, and some had chronic diseases. As shown in the studies by Jakob Zierk et al. (Zierk et al., 2020) and
Yang et al. (Yang et al., 2020), the leukocyte count was higher in males older than 50 years of age but lower in younger males, and the number of white blood cells increased in individuals with metabolic syndrome. The counts of leukocyte subsets, such as neutrophils, lymphocytes, and monocytes, increased with the BMI; however, the percentages of neutrophils and monocytes were inversely associated with BMI. In contrast, the percentage of lymphocytes was higher in individuals with a higher BMI. As a unique WBC subset, the lymphocyte percentage is higher in females than in males. The peripheral lymphocyte count reflects the capacity of the host immune response to predict the outcome of diseases (Afghahi et al., 2018; Semerano et al., 2019). Inconsistent conclusions have been reported on the difference in the absolute lymphocyte count between sexes. Wongkrajang et al. found that the lymphocyte count was higher in males, but the percentage was not different between sexes (Wongkrajang et al., 2018), which was opposite to our finding. Although the differences were not clinically relevant according to the Wongkrajang group, the peripheral lymphocyte percentage more accurately predicted the survival of patients with CRC than the peripheral lymphocyte count (Iseki et al., 2017). This inconsistent conclusion must be confirmed by conducting more studies in various fields.

Peripheral lymphocytes, neutrophils, and monocytes are the main subsets of white blood cells, and they play an important role in the individual’s immune system. This study revealed that white blood cell, neutrophil, and lymphocyte counts and percentages decreased with increasing age, while the monocyte count and percentage increased with ageing. An older age is also associated with a decreasing lymphocyte count (Lehtonen et al., 1990; Rea et al., 1996). Although its mechanism is not very clear, possible explanations may include age-related thymic involution, which leads to a change in the composition of lymphocyte subsets with age (Rea et al., 1996; Qin et al., 2016), and consequently, a change in overall immune competence (Linton & Dorshkind, 2004). With increasing age, the human body becomes relatively frail. The lymphocyte count, a marker of inflammation and immunosuppression, might be useful for identifying frail patients and evaluating people’s health conditions (Nunez et al., 2020).

Because the NLR and MLR are reliable systemic inflammatory markers, we tested their association with three common chronic diseases in a community population. As a result, the mean NLR and MLR in male patients with hypertension or diabetes was significantly greater than that in individuals without these diseases.

### Table 1. Characteristics of participants in the present study

| Variables | Male %/SD | Female %/SD | Total %/SD |
|-----------|-----------|-------------|------------|
| No.       | 4768      | 5796        | 10 564     |
| Age       |           |             |            |
| <60 years |           |             |            |
| ≥60 years |           |             |            |
| BMI       |           |             |            |
| <18.5     |           |             |            |
| ≥18.5     |           |             |            |
| ≥24.0     |           |             |            |
| ≥30       |           |             |            |
| Missing   |           |             |            |
| Hypertension |         |             |            |
| Presence  |           |             |            |
| Non-presence |       |             |            |
| Diabetes  |           |             |            |
| Presence  |           |             |            |
| Non-presence |       |             |            |
| Stroke    |           |             |            |
| Presence  |           |             |            |
| Non-presence |       |             |            |
| WBC Subset |         |             |            |
| WBC       |           |             |            |
| Neutrophil |           |             |            |
| Lymphocyte |           |             |            |
| Monocyte  |           |             |            |
| NLR       |           |             |            |
| MLR       |           |             |            |

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with hypertension, but not diabetes. We identified an association between an elevated NLR and a high risk of hypertension and diabetes, but not a risk of stroke. A dose–response relationship of NLR, MLR with hypertension is shown in a non-linear dose–response manner, but no significant relationship with stroke or diabetes. The MLR in this study was not a perfect indicator of chronic diseases, although a trend of a high MLR was associated with an insignificantly increased risk of hypertension and diabetes. Studies have identified the NLR as a risk indicator for overall and cause-specific mortality, such as cardiovascular disease and stroke (Kim et al., 2018; Fest et al., 2019; Maestrini et al., 2020). Neutrophils were first considered the major arm of the innate immune system. Recently, accumulating evidence has suggested that neutrophils are able to regulate many processes, such as acute

Table 2. Levels of NLR, MLR in participants with and without specific-complication

| Diseases | Female | | | | Male | | | |
|----------|--------|---|---|---|--------|---|---|---|
|          | Without | With | P-value | Without | With | P-value | | |
| Hypertension | | | | | | | | |
| NLR | 1.67 (1.29, 2.09) | 1.70 (1.34, 2.15) | 0.001 | 1.80 (1.41, 2.34) | 1.88 (1.45, 2.44) | 0.001 |
| MLR | 0.11 (0.08, 0.14) | 0.11 (0.08, 0.15) | <0.001 | 0.14 (0.10, 0.18) | 0.14 (0.11, 0.19) | 0.016 |
| Diabetes | | | | | | | | |
| NLR | 1.64 (1.29, 2.09) | 1.78 (1.37, 2.26) | <0.001 | 1.83 (1.43, 2.38) | 1.88 (1.42, 2.53) | 0.179 |
| MLR | 0.11 (0.08, 0.14) | 0.11 (0.08, 0.15) | 0.021 | 0.14 (0.10, 0.19) | 0.14 (0.11, 0.19) | 0.887 |
| Stroke | | | | | | | | |
| NLR | 1.67 (1.31, 2.12) | 1.76 (1.48, 2.30) | 0.114 | 1.84 (1.43, 2.39) | 1.79 (1.60, 2.85) | 0.191 |
| MLR | 0.11 (0.08, 0.15) | 0.13 (0.09, 0.17) | 0.045 | 0.14 (0.11, 0.19) | 0.15 (0.10, 0.20) | 0.558 |
injury and repair, cancer, autoimmunity, and chronic inflammation (Liew & Kubes, 2019). Inflammation has been confirmed to be associated with the risk of developing hypertension, diabetes, and stroke (Lontchi-Yimagou et al., 2013; Tsounis et al., 2014; Anrather & Iadecola, 2016). The NLR potentially reflects the balance between innate (i.e., neutrophils) and acquired (i.e., lymphocytes) immune responses in the body (Rucker et al., 2018). Therefore, the NLR is widely confirmed to be a potential

### Table 3. Estimation the risk of hypertension, diabetes and stroke exposure in different levels of NLR and MLR

| Factors | No. | Hypertension | | Diabetes | | Stroke | |
|---|---|---|---|---|---|---|---|
| | | OR | 95% CI | P-value | OR | 95% CI | P-value | OR | 95% CI | P-value |
| Age (≥ 60/< 60) | 3943/6417 | 1.82 | 1.67, 1.98 | <0.001 | 1.55 | 1.39, 1.74 | 0.00 | 1.85 | 1.14, 3.00 | 0.01 |
| Sex (M/F) | 4678/5702 | 0.85 | 0.78, 0.93 | <0.001 | 0.95 | 0.85, 1.06 | 0.34 | 1.38 | 0.89, 2.14 | 0.15 |
| BMI | | <0.001* | | | | | | 0.532* |
| <18.5 | 198 | 1.00 | reference | | 1 | reference | | 1 | reference | 0.532* |
| 18.5 | 4092 | 2.01 | 1.44, 2.8 | <0.001 | 2.87 | 1.51, 5.46 | <0.001 | 1.85 | 0.25, 13.59 | 0.54 |
| 24 | 5357 | 3.52 | 2.53, 4.91 | <0.001 | 4.30 | 2.27, 8.18 | <0.001 | 1.77 | 0.24, 12.92 | 0.58 |
| 30 | 733 | 5.33 | 3.72, 7.64 | <0.001 | 5.70 | 2.94, 11.03 | <0.001 | 0.82 | 0.08, 7.91 | 0.86 |
| NLR | | 0.003* | | | | | | | |
| <1.36 | 2590 | 1 | reference | | 1 | reference | | 1 | reference | 0.342* |
| 1.36 | 2595 | 1.08 | 0.96, 1.21 | 0.20 | 1.03 | 0.88, 1.2 | 0.74 | 2.33 | 1.18, 4.61 | 0.02 |
| 1.74 | 2597 | 1.14 | 1.02, 1.29 | 0.02 | 1.15 | 0.98, 1.35 | 0.08 | 1.60 | 0.76, 3.36 | 0.21 |
| 2.25 | 2598 | 1.19 | 1.05, 1.35 | 0.01 | 1.40 | 1.19, 1.66 | <0.001 | 1.98 | 0.94, 4.18 | 0.07 |
| MLR | | 0.183* | | 0.335* | | | | 0.534* |
| <0.089 | 2580 | 1 | reference | | 1 | reference | | 1 | reference |
| 0.089 | 2583 | 1.15 | 1.03, 1.29 | 0.01 | 0.91 | 0.78, 1.06 | 0.22 | 0.48 | 0.23, 1.00 | 0.05 |
| 0.121 | 2575 | 1.10 | 0.98, 1.24 | 0.12 | 0.88 | 0.75, 1.04 | 0.13 | 0.92 | 0.49, 1.70 | 0.78 |
| 0.164 | 2642 | 1.13 | 0.99, 1.28 | 0.07 | 0.92 | 0.77, 1.09 | 0.32 | 1.10 | 0.58, 2.10 | 0.78 |

* Asterisk stands for P-value for trend

### Figure 3. Restricted cubic spline plot of the risk of chronic diseases according to NLR and MLR. Odd ratios (OR) were adjusted for age, sex, and BMI.
biomarker for health conditions. In the present study, the NLR was increased in patients with hypertension and diabetes compared with the common population. Therefore, we postulate that the NLR is useful for screening chronic diseases amongst community residents. The value of the capacity of the MLR to evaluate health conditions requires further study.

Limitations

This study has unavoidable limitations. First, the sample source were residents of a single community, leading to limited representativeness. Second, the distribution of leukocyte subsets in the 40-year-old or younger group showed an unstable trend, and one potential reason may be that the young persons (38.52% of the total) who were recruited had a lower composition. The causal role of the NLR or MLR in hypertension or diabetes was unable to be determined because the data were obtained from a cross-sectional study. Hence, future studies are needed amongst additional communities that investigate younger participants, as well as cohort studies.

Conclusions

Based on these findings, leukocyte counts and leukocyte subset counts had different distributions in populations stratified by sex, age, and BMI. In summary, elevated leukocyte subsets are mostly present in older, fatter, and male populations. The NLR will be considered as a potential biomarker to evaluate the risk of chronic diseases, especially hypertension and diabetes.

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Ethical standard. The study was carried out in accordance with the recommendations of Ethikkommission der Universität Ulm, Ulm, Germany.

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