**INTRODUCTION**

Bilirubin is generally considered to be an end-stage product of heme metabolism. However, it has now been suggested to possess a number of crucial properties for the human body. For instance, it is a potent antioxidant as well as an anti-inflammatory factor that is capable of scavenging various reactive oxygen species and free radicals (1,2), as well as countering oxidative stress (3,4). Many epidemiological studies have observed an inverse relationship between bilirubin and a number of pathological abnormalities, such as cardiovascular diseases (5), metabolic syndrome (6), dyslipidemia (7), and diabetes (8,9). However, we retrieved only two previous investigations studying the association between bilirubin and white blood cell (WBC) count, and there was some discordance (10,11). Tsai et al. (10) analyzed 2458 apparently healthy adults in Taiwan and found that a higher level of serum total bilirubin (TB) was associated with a lower level of serum total bilirubin (TB) was associated with a lower WBC count, regardless of other classic cardiovascular risk factors. In the second paper, which was from Australia, Badrick et al. (11) analyzed two groups of individuals. After the removal of patients with an elevated WBC count and TB level, the community-living patients showed a negative correlation between the two, but the intensive care unit patients showed no significant relationship. In this study, we intended to systematically evaluate the relationship between TB level and WBC count in a large cohort of Chinese individuals, paying special attention to the sex differences in the relationship.

**METHODS**

**Design and recruitment**

A cross-sectional, community-based health check-up investigation was conducted in our hospital with the collaboration of a multidisciplinary team over a period of 10 years.
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Zhang L et al. Bilirubin and WBC count (ORs) for leucopenia with 95% confidence intervals (CIs) estimated by the chi-square test. Crude and adjusted odds ratios intergroup frequency differences in leucopenia were examined. Then, the TB concentration was divided into quartiles. The independent relationship between WBC count and TB was analyzed using binary logistic regression models. We conducted the statistical analyses with Statistical Package for Social Sciences software (SPSS version 17.0, Chicago, IL, USA). Significance was indicated by a p-value less than 0.05.

RESULTS

Characteristics of the participants according to sex

There were differences among the parameters with respect to sex (Table 1). Males were older than females. Most of the parameters, including age, BMI, SBP, DBP, ALT, TB, BUN, Cr, UA, TGs and WBCs, were significantly higher in males than in females. The TC concentration was significantly lower in males than in females.

Correlations between TB and other key variables

TB demonstrated significant negative relationships with most of the other variables, including age, BMI, BUN, UA, TC, TGs, FG and WBCs in men, as well as age, BMI, SBP, DBP, BUN, TC, TGs, FG and WBCs in women (Table 2).

Table 1 - Participant characteristics.

| Parameter      | Males          | Females        | T value |
|----------------|----------------|----------------|---------|
| Case number    | 29259          | 31832          |         |
| Age (years)    | 49.10 ± 12.56  | 47.45 ± 13.06  | 15.824**|
| BMI (kg/m²)    | 25.68 ± 3.18   | 23.97 ± 3.47   | 62.901**|
| SBP (mmHg)     | 125.57 ± 16.81 | 121.13 ± 18.24 | 31.271**|
| DBP (mmHg)     | 80.48 ± 11.17  | 74.70 ± 10.26  | 66.748**|
| ALT (U/L)      | 25.06 ± 13.61  | 18.41 ± 10.69  | 67.438**|
| TB (µmol/L)    | 13.37 ± 5.32   | 11.14 ± 4.52   | 55.943**|
| BUN (mmol/L)   | 5.09 ± 1.17    | 4.41 ± 1.22    | 67.262**|
| Cr (µmol/L)    | 78.73 ± 11.64  | 59.79 ± 9.58   | 220.320**|
| UA (µmol/L)    | 357.77 ± 74.99 | 263.93 ± 59.84 | 171.599**|
| TC (mmol/L)    | 5.10 ± 0.94    | 5.22 ± 1.03    | -14.718**|
| TGs (mmol/L)   | 1.73 ± 1.31    | 1.27 ± 0.86    | 51.581**|
| FG (mmol/L)    | 5.35 ± 1.22    | 5.06 ± 0.93    | 33.806**|
| WBCs (× 10⁹/L)| 5.72 ± 1.18    | 5.38 ± 1.11    | 37.084**|

BMI=body mass index, SBP=systolic blood pressure, DBP=diaastolic blood pressure, ALT=alanine aminotransferase, TB=total bilirubin, BUN=blood urea nitrogen, Cr=creatinine, UA=uric acid, TC=total cholesterol, TGs=triglycerides, FG=fasting glucose, WBCs=white blood cells.

*p < 0.01 (analyzed by the independent sample's t test).

Table 2 - Pearson bivariate correlations between TB and other variables according to sex.

| Parameter       | Correlation coefficients for males | Correlation coefficients for females |
|-----------------|-----------------------------------|-------------------------------------|
| Age             | -0.016**                          | -0.012*                             |
| BMI             | -0.059**                          | -0.081**                            |
| SBP             | -0.003                            | -0.018**                            |
| DBP             | 0.002                             | -0.013*                             |
| ALT             | 0.007                             | 0.025**                             |
| BUN             | -0.060**                          | -0.036**                            |
| Cr              | 0.044**                           | 0.041**                             |
| UA              | -0.016**                          | 0.005                               |
| TC              | -0.046**                          | -0.020**                            |
| TGs             | -0.100**                          | -0.069**                            |
| FG              | -0.058**                          | -0.061**                            |
| WBCs            | -0.123**                          | -0.059**                            |

TB=total bilirubin, BMI=body mass index, SBP=systolic blood pressure, DBP=diaastolic blood pressure, ALT=alanine aminotransferase, BUN=blood urea nitrogen, Cr=creatinine, UA=uric acid, TC=total cholesterol, TGs=triglycerides, FG=fasting glucose, WBCs=white blood cells.

*p < 0.05, **p < 0.01.

Ethics

The ethical, methodological and protocol aspects of this study were approved by the institutional review board and ethics committee of Tianjin Medical University General Hospital. We confirmed that all methods in the current study were conducted in compliance with the relevant guidelines and regulations. Written consent was provided by all participants in this research.

Measurements

Fasting blood tests and anthropometric measurements of all participants were conducted during their visits to our institution. Measurements of body height (BH) in centimeters, body weight (BW) in kilograms, and body mass index (BMI) by dividing BW (kilograms) by the square of BH (meters²) were performed. The determination of systolic blood pressure (SBP) and diastolic blood pressure (DBP) was performed by using a sphygmomanometer. Biochemical indicators included ALT, TB, blood urea nitrogen (BUN), creatinine (Cr), uric acid (UA), total cholesterol (TC), triglycerides (TGs), and fasting glucose (FG), which were determined by an autoanalyzer (Hitachi Corporation, Tokyo, Japan). WBC count was measured on a hemocytometer analyzer (Sysmex Corporation, Kobe, Japan).

The laboratory calibration references for the parameters were as follows: ALT 5-40 U/L, TB 3.4-20 µmol/L (0.20-1.17 mg/dL), BUN 1.7-8.3 mmol/L, Cr 44-115 µmol/L, TC 3.59-5.18 mmol/L, TGs 0.57-1.70 mmol/L, FG 3.6-5.8 mmol/L, and WBC count 4.0-9.5 × 10⁹/L.

Statistics

Data from men and women were analyzed separately. First, an independent sample’s t test was performed to measure differences in the indices. Pearson bivariate correlations were analyzed among TB and other parameters. Linear logistic regression analysis was performed to assess the independent relationship between WBC count and TB. Adjustments were performed for possible confounding factors, including age, BMI, SBP, DBP, TC, TGs and FG. Then, the TB concentration was divided into quartiles. The intergroup frequency differences in leucopenia were examined by the chi-square test. Crude and adjusted odds ratios (ORs) for leucopenia with 95% confidence intervals (CIs) were analyzed using binary logistic regression models. We conducted the statistical analyses with Statistical Package for Social Sciences software (SPSS version 17.0, Chicago, IL, USA). Significance was indicated by a p-value less than 0.05.
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Table 3 - Incidence of leucopenia in different sex by TB quartiles.

| Quartile   | Male          | Female         |
|------------|---------------|----------------|
|            | Crude OR (CI)* | Adjusted OR (CI)** | Crude OR (CI)* | Adjusted OR (CI)** |
| TB Quartile 1 | ≤9.60 (μmol/L, reference) |                  | ≤8.00 (μmol/L, reference) |                  |
| TB Quartile 2 | 9.60 < TB < 12.50 | 1.341 (1.122-1.603)** | 1.285 (1.074-1.537)** | 1.150 (1.022-1.294)* | 1.088 (0.965-1.226) |
| TB Quartile 3 | 12.50 < TB < 16.10 | 1.557 (1.308-1.853)** | 1.467 (1.231-1.748)** | 1.30 < TB < 13.40 | 1.245 (1.109-1.398)** | 1.137 (1.011-1.279)* |
| TB Quartile 4 | ≥16.10 | 1.799 (1.519-2.131)** | 1.600 (1.349-1.898)** | ≥13.40 | 1.280 (1.139-1.437)** | 1.135 (1.009-1.277)* |

Table 4 - The risks of leucopenia according to TB quartiles in different sex.

| TB Quartile | Males | Females |
|-------------|-------|---------|
|              | TB values | Crude OR (CI)* | Adjusted OR (CI)** | TB values | Crude OR (CI)* | Adjusted OR (CI)** |
| TB Quartile 1 | ≤9.60 (μmol/L, reference) |                  | ≤8.00 (μmol/L, reference) |                  |
| TB Quartile 2 | 9.60 < TB < 12.50 | 1.341 (1.122-1.603)** | 1.285 (1.074-1.537)** | 1.150 (1.022-1.294)* | 1.088 (0.965-1.226) |
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| TB Quartile 4 | ≥16.10 | 1.799 (1.519-2.131)** | 1.600 (1.349-1.898)** | ≥13.40 | 1.280 (1.139-1.437)** | 1.135 (1.009-1.277)* |

Table 5 - Correlations of leucopenia with different TB quartiles according to sex.

| TB Quartile | Males | Females |
|-------------|-------|---------|
|              | TB values | Crude OR (CI)* | Adjusted OR (CI)** | TB values | Crude OR (CI)* | Adjusted OR (CI)** |
| TB Quartile 1 | ≤9.60 (μmol/L, reference) |                  | ≤8.00 (μmol/L, reference) |                  |
| TB Quartile 2 | 9.60 < TB < 12.50 | 1.341 (1.122-1.603)** | 1.285 (1.074-1.537)** | 1.150 (1.022-1.294)* | 1.088 (0.965-1.226) |
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| TB Quartile 4 | ≥16.10 | 1.799 (1.519-2.131)** | 1.600 (1.349-1.898)** | ≥13.40 | 1.280 (1.139-1.437)** | 1.135 (1.009-1.277)* |

DISCUSSION

In mammals, due to the activities of the heme oxygenase and biliverdin reductase enzymes, bilirubin is produced during the physiological breakdown of heme. Bilirubin is not water soluble and requires a series of metabolic reactions for its further excretion, beginning with its binding to albumin. For decades, bilirubin has been viewed as an excretory product and a potentially toxic metabolite of heme metabolism that does not exert physiological benefits in humans. In particular, hyperbilirubinemia is generally viewed as a negative phenomenon because infants with jaundice are associated with kernicterus, and adults with jaundice are the harbingers of hepatic failure. However, over the span of human evolution, the production pathway of bilirubin has been consistently conserved. The teleological supposition is that bilirubin plays unique roles with physiological importance (26). In fact, bilirubin has been discovered to possess...
beneficial effects for the human body at physiologic concentrations. For instance, bilirubin has demonstrated an astonishing potency to scavenge overproduced free radicals and can also exert anti-inflammatory functions and powerful immunosuppressive effects. In addition, it can produce direct effects upon cell signaling (1-4). For example, bilirubin has been proven to be more effective at protecting lipids from oxidation than other water-soluble antioxidants, such as glutathione (27). Serum bilirubin has also been demonstrated to be a major contributor to the total antioxidant capacity in blood plasma (28).

Systemic inflammation and oxidative stress are important mechanisms in the development of various metabolic abnormalities (4). The powerful antioxidant and anti-inflammatory capacities of bilirubin are reported to be the basis for protection against diseases such as cardiovascular diseases (5) and metabolic syndrome (6). In addition, the anti-inflammatory effect of bilirubin has been demonstrated in its protective role against rheumatoid arthritis (29) and colitis (28). Bilirubin has also shown to be an immunomodulator, which makes bilirubin helpful in the treatment of diseases such as multiple sclerosis (30), lupus erythematosus (31), and autoimmune encephalomyelitis (32). Several molecular pathways have been identified to explain the above mechanisms, for example, the nuclear factor kappa B (NF-kB) pathway (33) and the extracellular signal-regulated kinase 1/2 (ERK1/2) pathway (34,35).

Only two previous investigations have studied the relationship between TB and WBC count (10,11); the results in the study by Tsai et al. (10) were generally in agreement with our research. The advantages of the current study included the large number of participants and the comprehensive and robust statistical analyses plus an emphasis on sex differences. In our opinion, the probable mechanism for the negative relationship between TB and WBC count could be protean and complicated (10). First, negative correlations between TB and inflammatory markers are reported to exist, which could regulate WBC production (36). Second, an elevated WBC count could reflect enhanced cellular oxidative stress, which could lead to the consumption and even depletion of natural antioxidants, thus leading to a decrease in TB concentration (10). Third, metabolic abnormalities, such as metabolic syndrome, may be an important underlying link in the association between TB and WBC count. It is reported that people with an increased level of WBCs will have an elevated risk of metabolic syndrome development, which is possibly due to chronic inflammation (19). However, epidemiologic surveys have reported that TB was negatively correlated with a number of abnormalities, such as cardiovascular diseases (5) and metabolic syndrome (6). The proposed reason for this phenomenon is a regulatory effect derived from insulin resistance, which is the core proposed mechanism in metabolic syndrome pathogenesis (37). Finally, inflammatory responses could be suppressed by bilirubin due to its preventive effects on the migration of leukocytes into target tissues, which may be mediated by a disruption in vascular cell adhesion molecule-1-dependent cell signaling. Therefore, for example, bilirubin can prevent dextran sodium sulfate-induced colitis by inhibiting leukocyte migration across the vascular endothelium and by suppressing inducible nitric oxide synthase expression (38).

There are several limitations to our study. First, this study was cross-sectional, which does not allow for conclusions regarding causal relationships. Prospective and interventional investigations should be planned in the future. Second, we did not measure markers of inflammation in our population because of the budget shortage. Third, we measured blood parameters in only a single blood sample, and we did not confirm the results due to the budget shortage, which may have resulted in less-precise results than those obtained from repeated measurements. Fourth, serum TB may be influenced by a number of hereditary factors (39) or dietary habits (40), which were not fully analyzed in the current study. Finally, a number of the participants with various undetected confounding factors might not be aware of their medical conditions, which could influence our results.

### CONCLUSIONS

In conclusion, TB is inversely related to WBC count. High TB quartiles are associated with significant risks for leucopenia, and this risk was more obvious in men than in women. It seems reasonable to suggest the assessment of WBC count when abnormal TB levels are found. The exact reason behind this association still requires further investigation.

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### AUTHOR CONTRIBUTIONS

Meng Z, Gong L and Zhang Q designed the investigation. Zhang L, Zhang C, Meng Z, Pang C, Liu X, Jia Q and Song K conducted the investigation and collected the data. Zhang L, Zhang C and Meng Z performed the statistical analysis. Zhang L, Zhang C, Meng Z and Pang C wrote the main manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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