The tissue factor expression on CD14++CD16-monocytes is a new markers in the Chinese Han older adult population with sepsis: A prospective study

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ABSTRACT

Objective: To investigate the tissue factor (TF) expression on different subsets of monocyte and tissue factor secretion of peripheral blood and evaluate their association with the prognosis of sepsis in the Chinese older adult population.

Methods: Monocyte subsets and TF expression on different subsets of monocyte were measured using flow cytometry in 80 older adult sepsis patients and 40 age and sex matched healthy controls. Plasma level of TF was measured using ELISA (enzyme-linked immunosorbent assay) method.

Results: TF expression on CD14++CD16− (MO1) monocyte was lower in death (28-day non-survivor) group compared with survival (28-day survivor) groups [1.01 % (0.58 %, 1.62 %) vs. 3.66 % (1.32 %, 6.93 %), p = 0.001]. The plasma level of TF was increased in death group compared to survival group according to the 28-day mortality [109.2 (67.3, 154.2) vs. 62.1 (44.7, 115.5) pg/mL, p = 0.031]. Logistic regression analysis showed TF expression on MO1 monocyte (β = −0.776, OR = 0.460, CI: 0.251, 0.843, p = 0.012) was independently associated with the 28-day mortality. The ROC (receiver operating characteristic) curve showed that the AUC (area under the curve) of the TF expression on MO1 monocyte for predicting 28-day mortality was 0.846 (p < 0.001).

Conclusion: The TF expression on CD14++CD16− monocyte is a new marker for the prognosis of older adult sepsis.

1. Introduction

Sepsis is a life-threatening infection with severe organ dysfunction that initiates a complex interplay between host inflammatory response and injury to the endothelial cells of the microvasculature (van der Poll et al., 2017). The resultant damage of endothelial cells leads to the activation of coagulation system and the inhibition of the normal fibrinolytic system, finally resulting in microvascular thrombosis followed by DIC (disseminated intravascular coagulation) and impaired organ perfusion and eventually death (van der Poll et al., 2017; Osuchowski et al., 2012; Prucha et al., 2017). There is ample evidence that revealed a wide-ranging cross-talk between hemostasis and inflammation, which is probably implicated in the pathogenesis of organ dysfunction in patients with sepsis. Inflammation not only leads to initiation and propagation of coagulation activity, but coagulation also markedly influences inflammation.

Tissue factor (TF) is a glycoprotein expressed on cell surface as a transmembrane receptor in various cells in the vasculature (Abraham et al., 2003), which has thrombogenic activity by effectively combining coagulation factor such as coagulation factor VII, IX, and X, lead to the...

Abbreviations: TF, tissue factor; ELISA, enzyme-linked immunosorbent assay; ROC, receiver operating characteristic; AUC, under the curve; DIC, disseminated intravascular coagulation; ED, emergency department; SOFA, sequential organ failure assessment; EDTA, ethylenediaminetetraacetic acid; TNF, tumor necrosis factor; IL, interleukin; SASP II, simplified acute physiology II; PCT, procalcitonin; CRP C, reactive protein; ESR, erythrocyte sedimentation rate; LPS, lipopolysaccharide.

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formation of thrombin (ten Cate, 2000; Levi et al., 2004). Monocytes are considered to be the main source of TF (Kasthuri et al., 2009), and are dynamic immune modulatory cells that change during different disease status and age groups. Human monocytes comprise a heterogeneous population that can be classified into three subsets based on CD14 (lipopolysaccharide receptor) and CD16 (FcγIII receptor) expression on their cell membranes (Ziegler-Heitbrock et al., 2010; Lund et al., 2016). According to this classification, monocytes are divided into “classical monocytes” with strong expression of CD14 and negative expression of CD16 (CD14++;CD16−), “intermediate monocytes” that express both receptors (CD14++;CD16+), and “nonclassical monocytes” expressing predominantly CD16 (CD14+CD16++) (Ziegler-Heitbrock et al., 2010). Previous studies on sepsis and monocyte seldom distinguish age groups, and there are few studies on sepsis and monocyte functions in the older adult population. Based on previous research recommendations that new markers used for human monocyte subsets should combine with these established markers (Ziegler-Heitbrock et al., 2010), we then comparing the TF expression on cell surface among the three known subtypes of monocyte to study the monocyte subsets and plasma level of TF in patients with sepsis in Chinese older adult population.

2. Methods

2.1. Patients and control subjects

The patients in this study were admitted to the emergency department (ED) of two Hospitals (Beijing Chao-Yang Hospital and Beijing Shijitan Hospital), with approximately 250,000 and 100,000 ED admissions per year, respectively. The patients included were aged ≥ 65 years and diagnosed with sepsis defined by the 2016 International Diagnostic Criteria for Sepsis 3.0, (Singer et al., 2016) organ dysfunction is indicated by an increase in the Sequential Organ Failure Assessment (SOFA) score by ≥ 2 points for clinical operationalization, and patients with septic shock are clinically identified by a vasopressor requirement to maintain a mean arterial pressure of ≥ 65 mm Hg and plasma lactate level of ≥ 2 mmol/L (>18 mg/dL) in the absence of hypovolemia. The exclusion criteria were (a) congenital and/or acquired immunodeficiency diseases, (b) long-term use of corticosteroids or immunosuppressive drugs, (c) patients with HIV infection or cancer, (d) death within 2 days of the onset of septic shock, signs of sepsis occurring >3 days prior to admission, (e) declined to participate. A healthy control group was included in the physical examination centres of the two hospitals and excluded if they had hypertension, coronary heart disease, diabetes, or other serious diseases of the heart, brain, lung, liver, or kidney. Blood samples were collected on the same day as admission to the physical examination centre.

Table 1 Baseline characteristics of the patients.

| All patients | Controls | p value |
|--------------|----------|---------|
| Septic shock | Septic   |         |
| Number       | 28       | 52      | 40      |
| Age (years)  | 80.00 ± 8.38 | 81.10 ± 8.59 | 76 ± 5.75 | 0.085 |
| Male, n (%)  | 17 (60.7) | 26 (50) | 24 (40) | 0.530 |
| Type of infection, n (%) | | | | |
| Pneumonia    | 22 (78.6) | 33 (63.5) | / |
| USI          | 2 (7.1)  | 11 (21.2) | / |
| BTI          | 4 (14.3) | 8 (15.4) | / |
| WBC (>10^9/L) | 10.86 (6.92, 16.36) | 11.61 (7.24, 17.62) | / |
| MO (>10^9/L) | 0.44 (0.23, 0.61) | 0.46 (0.33, 0.76) | / |
| MOP (%)      | 3.60 (2.13, 6.68) | 4.50 (3.20, 6.10) | / |
| PCT (ng/mL)  | 18.83 ± 40.44 | 11.50 ± 23.00 | / |
| CRP (mg/L)   | 140.25 ± 120.5 ± 81.09 | 110.59 ± 79.48 | / |
| ESR (mm/h)   | 50.00 ± 33.79 | 51.36 ± 31.88 | / |
| D-dimmer (ng/mL) | 1722 (715, 3680) | 1118 (377, 3180) | / |
| SOFA score   | 11.07 ± 1.39 | 5.33 ± 2.36 | <0.001 |
| SAPS II      | 45.50 ± 10.47 | 37.61 ± 8.94 | / |
| 28-day mortality, n (%) | 7 (25.0) | 5 (9.6) | 0.003 |

Data are mean ± SD, median (Q1, Q3), number (%); USI urinary system infection; BTI biliary tract infection; WBC white blood cell count; MO blood monocyte count; MOP blood monocyte percentage; PCT procalcitonin; CRP C reactive protein; ESR erythrocyte sedimentation rate; SOFA sequential organ failure assessment; SAPS II simplified acute physiology score II.
(caption on next page)
2.2. Data collection

A total of 4 mL peripheral blood samples were collected within 24 h after the sepsis criteria were met. The clinical characteristics of patients, including age, sex, and laboratory examination results, were recorded after the onset of sepsis. The SOFA score was calculated based on related clinical and demographic data. During follow-up, the following data were collected: type of infection (pneumonia, urinary system infection, and biliary tract infection) and outcome after 28 days (survival or death). This study was conducted in compliance with the Declaration of Helsinki and approved by the institutional ethics committees of the two Hospitals. All participants provided written informed consent aforesaid by themselves or their direct relative (When these older adult patients with sepsis are unable to sign the informed consent by themselves due to their illness such as neurological symptoms, we contact their immediate family members to obtain their consent and sign the informed consent).

2.3. Flow cytometry

Analysis was performed within 2 h when collected into ethylenediaminetetraacetic acid (EDTA) anticoagulant tubes on whole blood cells. After erythrocytes were lysed with lysing solution (BD Bioscience, San Jose, CA, USA). All antibodies were previously titered and optimized depending on the fluorophore used. These trends were not significant in our study. Additionally, there were no significant differences in D-dimmer, total number of peripheral blood leukocytes, monocytes count and so on between the groups.

2.4. Cytokine testing

Peripheral venous blood samples from each participant were collected in potassium EDTA-containing tubes and were centrifuged at 3000g for 10 min at ambient temperature immediately. Plasma was extracted and frozen at −80 °C until analysis. Plasma concentrations of TF were measured by ELISA (enzyme-linked immunosorbent assay) from a commercially available microplate kit (Abcam Co. Ltd) in accordance with the manufacturer’s instructions. The intra- and inter-assay coefficients of variation were both <5%.

2.5. Statistical analysis

Descriptive statistics, including the mean and standard deviation for normally distributed data or the median and interquartile range for non-normally distributed data, were used to describe the cohort. Normality was processed using the Kolmogorov-Smirnov and Shapiro-Wilk test according to the sample of groups. Comparisons of baseline characteristics related to patients and controls were performed using independent sample t-tests, Mann–Whitney U tests, chi-square and Kruskal-Wallis tests as appropriate. Comparisons of monocyte subsets and plasma cytokine levels between groups were assessed using Mann–Whitney U tests and multiple binary logistic regression was used to identify variables associated with the 28-day mortality. The area under the curve (AUC) of receiver operating characteristic (ROC) curves was used to compare the prediction of 28-day mortality in sepsis. All statistical tests were two-tailed, and statistical significance was set at p < 0.05. All data were analyzed using SPSS 23.0 software.

3. Results

3.1. Patient characteristics

A total of 80 patients were enrolled after screening 105 patients with sepsis age > 65 years Chinese Han population (Fig. 1). Of these, there were 80 Patients including 28 with septic shock and 52 without shock (septic group) according to disease severity, from November 2019 to December 2020 were enrolled in the end. Forty healthy subjects from a physical examination centre matched for sex, age, and race were included in this study. The demographic and clinical characteristics of patients are presented in Table 1. Higher SOFA and Simplified Acute Physiology (SAPS) II scores in septic shock patients indicated more severe disease. In addition, patients in the septic shock group had higher 28-day mortality than those without shock. Although traditional clinical inflammatory markers, such as procalcitonin and C-reactive protein, were both higher in septic shock patients than in those without shock, these trends were not significant in our study. Additionally, there were no significant differences in D-dimmer, total number of peripheral blood leukocytes, monocytes count and so on between the groups.

3.2. TF expression of three monocyte subsets among different groups

Peripheral blood monocyte subsets were defined as MO1 (classical, CD14++CD16−), MO2 (intermediate, CD14++CD16+), and MO3 (non-classical, CD14+CD16+) according to the expression of CD14 and CD16. The percentages of the three subsets among the groups were shown in Fig. 2. The percentage of MO1 monocyte was higher in septic shock group comparing to those without shock (septic group) [68.8 % (50.7 %, 77.8 %) vs. 40.8 % (19.7 %, 70.7 %), p = 0.011] and the percentage of MO3 monocyte was higher in sepsis patients than in controls [3.1 % (1.7 %, 5.7 %) vs. 1.9 % (0.9 %, 4.4 %), p = 0.034]. While there was no significant difference among other groups; we found that TF expression on MO1 monocyte was lower in death (28-day non-survivor) group compared with survival groups (28-day survivor) [1.01 % (0.58 %, 1.62 %) vs. 3.66 % (1.32 %, 6.93 %), p = 0.001]. But, the TF expression on MO1 monocyte between patients and controls, septic shock and septic, death and survival according to 28-day mortality were not significant difference. The detailed data are shown in Fig. 3.
Fig. 3. Box-plot illustrated the TF expression on the three kinds of monocyte subsets. Data are shown as box plot with medians (lines inside boxes), 25th and 75th quartiles (limits of boxes) and range with whiskers. a, b, c represents TF expression on MO1 (CD14++CD16+), MO2 (CD14++CD16+), and MO3 (CD14+CD16++) monocyte among patients (n = 80) and controls (n = 40), septic shock (n = 28) and septic (sepsis without shock, n = 52), death (28-day non-survivor, n = 12) and survival (28-day survivor, n = 68) groups respectively. Only TF expression on MO1 monocyte between death and survival is significant different [1.01 % (0.58 %, 1.62 %) vs. 3.66 % (1.32 %, 6.93 %), p = 0.001]. Other groups patients and controls [MO1: 3.26 % (0.96 %, 5.15 %) vs. 4.01 % (1.61 %, 6.46 %), p = 0.172; MO2: 6.63 % (3.18 %, 15.10 %) vs. 7.58 % (3.31 %, 14.40 %), p = 0.955; MO3: 7.22 % (4.54 %, 18.53 %) vs. 13.30 % (5.81 %, 25.00 %), p = 0.079], septic shock and septic [MO1: 1.69 % (0.78 %, 5.09 %) vs. 3.33 % (1.25 %, 5.50 %), p = 0.178; MO2: 6.98 % (3.39 %, 12.73 %) vs. 6.13 % (2.98 %, 16.68 %), p = 0.789; MO3: 6.91 % (3.43 %, 12.63 %) vs. 7.82 % (4.54 %, 19.56 %), p = 0.518] were not significant different.
mortality. We found that the plasma level of TF was increased in death group compared to survival group [109.2 (67.3, 154.2) vs. 62.1 (44.7, 115.5), p = 0.031] (Fig. 4c), while the plasma level of TF in all sepsis patients was not significant different comparing with control group [68.6 (45.3, 112.6) vs. 83.3 (32.9, 131.3), p = 0.787] (Fig. 4a), and the plasms level of TF in septic shock patients was not significant different than in sepsis without shock (septic) group [109.2 (51.5, 132.3) vs. 62.7 (44.8, 97.9), p = 0.068] (Fig. 4b).

4. TF expression on MO1 monocyte as independent predictors of the 28-day mortality in older adult sepsis patients

Univariate analysis of TF expression on monocytes and plasma level of TF with the onset of septic shock did not show meaningful results. Multivariate analysis by logistic regression only shown SOFA score, one of the screened variables from univariate analysis, was the strong powerful predictor for septic shock after adjusting for confounding factors such as age and gender (Table 2). SOFA score was also an important factor for 28-day mortality in univariate analysis [18 (4.5, 23.0), 6 (4.0, 10.5), p < 0.001]. Other clinical characteristics between the death and survival groups were not significant difference including SAPSII (Table 3).

TF expression on the three monocyte subsets and plasma level of TF had exhibited significant results in the univariate analysis in 28-day mortality. In the subsequent multivariate logistic regression analysis, we found that TF expression on MO1 monocyte (β = −0.776, OR = 0.460, CI: 0.251, 0.843, p = 0.012) and SOFA score (β = 0.996, OR = 2.708, CI: 1.093, 6.706, p = 0.031) were independently associated with the 28-day mortality after adjusting for confounding factors such as age and gender (Table 4). The ROC curve showed that the AUC of the TF expression on MO1 monocyte for predicting 28-day mortality was 0.648 (p < 0.001) and the AUC of SOFA score was 0.748 (p < 0.001). The AUC for combination the percentage of TF expression on MO1 monocyte with SOFA score 0.799 (p = 0.003) which was higher than each parameter alone. The detailed data are presented in Fig. 5.

5. Discussion

Almost all immune cells variated with aging in the aspects of numbers or subsets which altered the functions of immune cells such as resulting in an increased susceptibility to infections that promote the emergence of age-associated sepsis. Classical monocytes (CD14++CD16–) we defined it as an MO1 monocyte in our research are prominent monocytes in healthy individuals (Calderon et al., 2017).
proliferative capacity of CD14++CD16− monocytes may decline with age in transcriptomic profiling (Wong et al., 2011) and the proportion of CD14++CD16− monocytes in older adults is reduced compared with that in younger adults (Pence and Yarbro, 2018). Our study demonstrated the proportion of CD14++CD16− monocyte was higher in older adult septic shock patients than those without shock group. Based on previous evidence that CD14++CD16− monocytes are pro-inflammatory cells due to their high abilities of secreting pro-inflammatory cytokines in response to microbial components (Cros et al., 2010). Our result just hinted the MO1 monocyte in older adult patients with sepsis can still play a pro-inflammatory role, but it is unknown whether this MO1 monocyte subset just only exhibit the pro-inflammatory activities due to the expression of other surface molecule in older adult patients.

TF is the transmembrane receptor for coagulation factor VII (FVII) and expressed generally at extravascular but may be induced on circulating monocytes and other immune cells by inflammatory cytokines or bacterial endotoxins (Semeraro and Colucci, 1997), and then be secreted from these immune cells as a component of plasma TF (Grover and Mackman, 2018). Monocytes exposed to lipopolysaccharide (LPS) in vitro or in vivo leads to a rapid and transient expression of TF (Drake et al., 1993; Franco et al., 2000). The expression of TF on the surface of circulating monocytes are increased due to the producing of pro-inflammatory cytokines, including TNF-α, IL-1, IL-6, and IL-8 in sepsis (Doshi and Marmur, 2002). Monocytes expressing TF were more likely to be polyfunctional cytokine producers, including TNF-α, IL-1β, and IL-6, when compared to those not expressing TF (Schechter et al., 2017). While, the individuals in different immune states presented entirely different TF expression on monocyte surface and TF secretion in plasma after LPS stimulation in vitro experiments (Egorina et al., 2005). Our study revealed that 28-day non-survivor patients had lower TF expression on CD14++CD16− monocyte than 28-day survivors. The down regulated TF expression on CD14++CD16− monocyte in older adult sepsis indicated that the non-survivor patients was in a state of low response at the beginning of the disease which was interpreted from a previous study that individuals in the low response state had significantly less ability of TF expression on monocytes after LPS stimulation than individuals in the high response state (Egorina et al., 2005). It is also proved that older adult sepsis patients with poor prognosis tend to have a low response in the balance between pro-inflammatory and anti-inflammatory response at the beginning of the sepsis. This may be an important feature of sepsis in the older adult population.

Age is associated with changes in the vasculature, hemostasis and coagulation systems, including alterations of platelets, plasma levels of blood coagulation proteins and fibrinolysis impairment which are all associated with a procoagulant state (Wilkerson and Sane, 2002; Franzini, 2006; Mari et al., 2008). This can lead to microvascular thrombosis more or less in older adult patients to some extent and would explain why did D-dimmer the traditional indicator for pro-coagulation show no significant differences between whether it was septic shock or not.
not and whether patient survival or dead according to 28-day mortality in our study. Sepsis is a complex inflammatory response involving the disorders of the coagulation system (van der Poll et al., 2017). Pro-inflammatory cytokines lead to activation of coagulation and down-regulate the physiologic anticoagulant pathways; conversely activated coagulation proteases modulate the inflammatory response furthermore (Levi and Ten Cate, 1999; Anas et al., 2010). Xue et al. demonstrated that the plasma level of TF in the non-survivors with severe sepsis were obviously higher than those in the survivors (Xue et al., 2015). This was consistent with our study about plasma TF level was higher in 28-day non-survivors comparing with survivors in older adult sepsis. The elevated levels of the blood coagulation cascade initiated from TF. However, it is inconsistent about the TF expression on CD14++CD16− monocyte between the two groups. Although monocyte is the main source of circulating TF, other cells such as endothelial and smooth muscle cells, fibroblasts also secret TF (Steffen et al., 2006). So, the inconsistent result indicated that although TF expression on CD14++CD16− monocyte is reduced, the ability of TF secretion from other cells is still powerful under the condition of sepsis with poor prognosis. Multivariate logistic regression analysis shown that TF expression on MO1 monocyte was a protective factor for 28-day mortality. In the following ROC curve analysis TF expression on MO1 monocyte did not only show the ability for predicting 28-day mortality, but also enhance the ability of SOFA score to evaluate the prognosis of older adult sepsis. This all directly or indirectly indicate that TF expression on CD14++CD16− monocyte is a good prognostic indicator for older adult patients with sepsis.

5.1. Limitations

Our study had several limitations. First, some results may not reflect the real situation because of the limited number of samples in this study. Therefore, the sample size should be increased in future research. Second, this study focused on TF expression on different monocyte subsets and TF secretion at the beginning of sepsis, but these may change with the progression of sepsis. Therefore, changes in TF expression on monocyte subsets and TF secretion throughout different stages of sepsis require further research. Third, a new model for determining the occurrence and development of sepsis in older adult patients that combines TF expression on monocyte subsets and TF secretion needs to be established in a future study.

6. Conclusions

Although previous studies on monocyte subsets and sepsis have obtained definite results, this is the first study on the association of TF expression on subsets of monocyte and TF secretion with the prognosis of sepsis in the older adult Chinese Han population aged >65 years. Population aging is becoming increasingly serious all over the world, an increasing number of older adult sepsis patients will admit to clinical department. Early diagnosis and judging the prognosis of these patients is a challenge for doctors. The TF expression on monocyte could be new markers for the prognosis of older adult sepsis and provide new insight for further treatment.

CRediT authorship contribution statement

QG and SBG designed the study. QG, LY and XYC acquired the data. QG performed the analysis and interpretation of data. QG wrote the manuscript. SBG and FT revised the manuscript.

Conflicts of interest

The authors have no conflicts of interest to declare.

Data availability

Data will be made available on request.

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