Original Article

Systemic immune-inflammation index in predicting hospitalized bronchiectasis exacerbation risks and disease severity

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Background: Bronchiectasis is a common respiratory disease with neutrophilic inflammation being the predominant pathophysiology. Systemic immune-inflammation index (SII) is a simple and readily available biomarker being studied in various conditions including asthma, chronic obstructive pulmonary disease, and interstitial lung disease, but not in bronchiectasis. We aim to investigate the prognostic role of SII in bronchiectasis with this study.

Methods: A retrospective cohort study in Chinese patients with non-cystic fibrosis (CF) bronchiectasis was conducted in Hong Kong, to investigate the association between baseline SII and of hospitalized bronchiectasis exacerbation risk over 4.5 years of follow-up, as well as correlating with disease severity in bronchiectasis. The baseline SII in 2018 was calculated based on stable-state complete blood count.

Results: Among 473 Chinese patients with non-CF bronchiectasis were recruited, 94 of the patients had hospitalized bronchiectasis exacerbation during the follow-up period. Higher SII was associated with increased hospitalized bronchiectasis exacerbation risks with adjusted odds ratio (aOR) of 1.001 [95% confidence interval (CI): 1.000–1.001, P=0.003] for 1 unit (cells/μL) increase in SII count and aOR of 1.403 (95% CI: 1.126–1.748, P=0.003) for 1 standard deviation (SD) increase in SII. SII was found to have significant negative association with baseline forced expiratory volume in the first second (FEV_1) (in litre and percentage predicted), forced vital capacity (FVC) in percentage; and significant positive correlation with the extent of bronchiectasis and baseline neutrophil to lymphocyte ratio (NLR).

Conclusions: SII could serve as biomarker to predict the risks of hospitalized exacerbation in bronchiectasis patients, as well as correlating with the disease severity.

Keywords: Bronchiectasis; bronchiectasis exacerbation; phenotype; systemic immune-inflammation index (SII); biomarkers

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Introduction

Bronchiectasis is one of the most common chronic airway diseases with neutrophilic inflammation as the predominant pathophysiological mechanism (1-4). Exacerbation is a common and consequential characteristic of bronchiectasis, in which European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC) Bronchiectasis Registry estimated that half of the bronchiectasis patients would have at least two exacerbations annually (5). Bronchiectasis exacerbation is well-reported to have negative impacts on the morbidity and quality of life, mortality of the patients,

and is also associated with higher healthcare costs (6-14). In Bronchiectasis Severity Index (BSI), hospitalized exacerbation is included as an important domain (6,15). On the other hand, FACED score [forced expiratory volume in 1 s (FEV_1), age, chronic colonization, extension, and dyspnea score] (using a combination of FEV_1, patient's age, the presence of *Pseudomonas aeruginosa* colonization, disease extent and degree of dyspnea to predict five-year all-cause mortality) (15) has also been validated to predict the risk of future exacerbations (16-18). Various inflammatory markers such as neutrophil to lymphocyte ratio (NLR) have been studied as potential prognostic biomarkers in bronchiectasis.

Systemic immune-inflammation index (SII) is one of the relatively new biomarkers that was developed in 2014, which is calculated using a simple formula as neutrophil × platelet / lymphocyte (19). SII has been studied in various conditions such as asthma (20), chronic obstructive pulmonary disease (21), interstitial lung disease (22), acute myocardial infarction (23), diabetes mellitus (24), Guillain-Barré syndrome (25), malignancies and vasculitis (26) as a biomarker of systemic inflammation with prognostic implication (27-32).

While SII is a readily available biomarker, there has not been any data on its role in bronchiectasis. In this study, we aim to investigate the role of baseline SII at stable-state in predicting risks of hospitalized bronchiectasis exacerbation, and the correlation of SII with various markers of disease severity in bronchiectasis. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1392/rc).

Highlight box

Key findings

- Higher systemic immune-inflammation index (SII) was associated with increased hospitalized bronchiectasis exacerbation risks.
- SII was negatively associated with baseline forced expiratory volume in 1 s and forced vital capacity, and positively correlated with the extent of bronchiectasis and baseline neutrophil to lymphocyte ratio (NLR).

What is known and what is new?

- SII is a simple and readily available biomarker being studied in various chronic respiratory diseases.
- The potential role of SII as a biomarker in prognostication of bronchiectasis is demonstrated in this study, especially on risks of hospitalized bronchiectasis exacerbation.

What is the implication, and what should change now?

- SII could serve as a biomarker to predict the risks of hospitalized exacerbation in patients with bronchiectasis, as well as correlating with the disease severity.

Methods

This was a retrospective single-center cohort study. All Chinese patients who were followed up in the respiratory clinic for non-cystic fibrosis (CF) bronchiectasis at the Department of Medicine, Queen Mary Hospital (QMH) were identified through the bronchiectasis database of the respiratory team. Patients were enrolled from 1/1/2018 to 31/12/2018. They were followed up till 30/6/2023. Patient clinical records for the subsequent 4.5 years were reviewed. Patients were excluded if they had traction bronchiectasis due to interstitial lung disease, bronchiectasis in allergic bronchopulmonary aspergillosis or defaulted follow-up. Demographic data, clinical data and investigations results were identified from the database. The primary outcome was bronchiectasis exacerbation that mandated hospitalization. Patients with bronchiectasis exacerbation who required in-patient care from 1/1/2019 to 30/6/2023 were identified from the electronic patient records (ePR) of the Hospital Authority, which is a territory-wide electronic medical record consisting of all in-patients, out-patients and emergency department visit records of all public hospitals and clinics in Hong Kong. Hospitalized bronchiectasis exacerbation was defined as (I) a deterioration of three or more key symptoms for at least 48 hours: cough, sputum volume and/or consistency, sputum purulence, dyspnea and/or exercise tolerance, fatigue and/or malaise, hemoptysis; and (II) a clinician's assessment that a change in bronchiectasis treatment was required (33), which necessitated hospitalization for management. SII at baseline was calculated by the formula: platelet × neutrophil lymphocyte.

QMH is a university-affiliated hospital and tertiary referral centre, with a designated bronchiectasis specialty clinic for. The clinic records and radiographic findings were reviewed by the investigators (W.C.K. and J.C.M.H.) to validate the diagnosis of bronchiectasis. Patients' clinical records were accessed through the ePR of the Hong Kong Hospital Authority, which is an electronic medical record comprising both out-patient and in-patient episodes. The information available included patient demographics, clinical notes, investigation results and treatments prescribed. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study

was approved by the Institutional Review Board of the University of Hong Kong and Hospital Authority Hong Kong West Cluster with approval number UW 20-435 and individual consent for this retrospective analysis was waived.

Statistical analysis

The demographic and clinical data were described in frequency or mean ± standard deviation (SD). Baseline demographic and clinical data were compared between the groups with or without exacerbation during follow-up period by independent *t*-tests. Logistic regression was used to estimate the association between SII and the hospitalized bronchiectasis exacerbation risks in the 4.5-year follow-up period. Baseline age, E-FACED score (exacerbation, FEV_1, age, chronic colonization, extension, and dyspnea score), gender and smoking status were adjusted as potential confounders. In sensitivity analysis, multivariate logistic regression was conducted by adjusting (I) factors that are significant in univariate logistic regression; (II) age, gender, smoking status and FACED score; and (III) age, gender, smoking status, and BSI. Relationship between SII and time to hospitalized bronchiectasis exacerbation was assessed by Cox regression. The relationship between SII, BSI, FACED score, E-FACED score, spirometry values and extent of bronchiectasis by number of lobes involved were assessed using the Pearson's correlation coefficient metrics. Statistical significance was determined at the level of P=0.05. All statistical analyses were performed using the 28th version of SPSS statistical package.

Results

A total of 473 Chinese patients with non-CF bronchiectasis managed in QMH were included. Ninety-four of them were hospitalized for bronchiectasis exacerbation in the 4.5-year follow-up period. The mean follow-up interval was 4.28±0.73 years.

Baseline characteristics

The mean age of the patients was 68.0±12.0 years. There were more females (67.7%) and never-smokers (80.1%). A total of 96 (20.3%) patients had *Pseudomonas aeruginosa* colonization. The mean FEV_1 was 1.69±0.64 L (84.5%±24.1%). Multi-lobar involvement (disease involved at least 3 lobes), was seen in 189 (40%) patients. The mean SII was (699±569)×10^9/L. The mean time for hospitalized bronchiectasis exacerbation was 22.2±17.2 months. The results are summarized in *Table 1*.

Factors associated with risks of hospitalized bronchiectasis exacerbation

The following factors are associated with risks of hospitalized bronchiectasis exacerbation in univariate logistic regression: age [odds ratios (OR): 1.029, 95% confidence interval (CI): 1.009–1.049, P=0.005], baseline FEV_1 by percentage predicted (OR: 1.026, 95% CI: 1.013–1.037, P<0.001), modified Medical Research Council (mMRC) dysnpoea scale (OR: 1.962, 95% CI: 1.162–3.314, P=0.01), history of bronchiectasis exacerbation in past 1 year (OR: 2.336–1.723–3.168, P<0.001), *Pseudomonas aeruginosa* colonization (OR: 3.449, 95% CI: 2.128–5.591, P<0.001), number of lobes involved (OR: 2.072, 95% CI: 1.342–3.200, P=0.001), baseline FACED score (OR: 1.582, 95% CI: 1.360–1.839, P<0.001), E-FACED score (OR: 1.613, 95% CI: 1.410–1.845, P<0.001) and BSI (OR: 1.238, 95% CI: 1.163–1.318).

Risk of hospitalized bronchiectasis exacerbation and baseline SII

Increased baseline SII was associated with increased hospitalized bronchiectasis exacerbation risks in the follow-up period with OR of 1.000 (95% CI: 1.000–1.001, P=0.007) for 1 unit increase in SII and OR of 1.316 (95% CI: 1.077–1.601, P=0.007) for 1 SD increase in SII. With multivariate logistic regression adjusted for age, gender, smoking status and E-FACED score, the adjusted OR (aOR) was 1.001 (95% CI: 1.000–1.001, P=0.003) for 1 unit (cells/μL) increase in SII count and aOR of 1.403 (95% CI: 1.126–1.748, P=0.003) for 1 SD increase in SII. Higher SII was also associated with shorter time to hospitalized bronchiectasis exacerbation with hazard ratio (HR) of 1.000 (95% CI: 1.000–1.001, P=0.002) in univariate analysis and adjusted HR of 1.000 (95% CI: 1.000–1.001, P=0.006) in multivariate analysis.

Baseline SII and correlation with other parameters of severity in bronchiectasis

Baseline SII was found to have a weak negative association with baseline FEV_1 in litre and percentage predicted, as well as forced vital capacity (FVC) in percentage predicted with

Table 1 Baseline demographic and clinical characteristics

Clinical and laboratory parameters	No exacerbation (n=379)	Hospitalized exacerbation during follow-up (n=94)	Whole cohort (n=473)	P value
Age (years), mean ± SD	67.2±11.7	71.5±12.3	68.0±12.0	0.001*
Male, n (%)	117 (30.9)	36 (38.3)	153 (32.3)	0.17
Ever-smoker, n (%)	74 (19.5)	20 (21.3)	94 (19.9)	0.70
FEV_1 (L), mean ± SD	1.75±0.62	1.48±0.67	1.69±0.64	0.002*
FEV_1 (% predicted), mean ± SD	87.4±21.4	74.3±29.9	84.5±24.1	<0.001*
FVC (L), mean ± SD	2.58±1.05	2.34±0.83	2.53±1.01	0.056
FVC (% predicted), mean ± SD	94.8±20.4	88.2±23.1	93.3±21.1	0.045*
FACED score, median [IQR]	1 [0–2]	2.5 [2–4]	2 [0–3]	<0.001*
E-FACED score, median [IQR]	2 [0–3]	3 [2–4]	2 [0–3]	<0.001*
Bronchiectasis Severity Index, median [IQR]	6 [4–8]	8 [7–12]	7 [4–9]	<0.001*
Extent of involvement ≥3 lobes, n (%)	138 (36.4)	51 (54.3)	189 (40.0)	0.002*
Pseudomonas aeruginosa colonization, n (%)	60 (15.8)	36 (38.3)	96 (20.3)	<0.001*
Exacerbations requiring hospitalization in past 12 months, n (%)	27 (7.1)	23 (24.5)	50 (10.6)	<0.001*
Baseline platelet count ($\times10^9$ cells/L), mean ± SD	246±73	251±76	247±73	0.53
Baseline neutrophil count ($\times10^9$ cells/L), mean ± SD	3.96±1.34	4.34±1.62	4.18±1.65	0.01*
Baseline lymphocyte count ($\times10^9$ cells/L), mean ± SD	1.77±0.63	1.69±1.08	1.74±0.61	0.23
Baseline SII ($\times10^9$/L), mean ± SD	659±480	853±815	699±569	0.003*
Co-morbidities, n (%)				
Hypertension	126 (33.2)	31 (33.0)	157 (33.2)	0.26
Diabetes mellitus	50 (13.2)	10 (10.6)	60 (12.7)	0.22
Ischemic heart disease	38 (10.0)	8 (8.5)	46 (9.7)	0.36
History of malignancies	59 (15.6)	18 (19.1)	77 (16.3)	0.14

*, statistically significant. SD, standard deviation; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; FACED score, FEV_1, age, chronic colonization, extension, and dyspnea score; IQR, interquartile range; E-FACED score, exacerbation, FEV_1, age, chronic colonization, extension, and dyspnea score; SII, systemic immune-inflammation index.

Pearson coefficient of –0.190 (P=0.001), –0.199 (P=0.001), and –0.167 (P=0.005) respectively. Baseline SII was found to have a weak positive correlation with the extent of bronchiectasis (in number of lobes involved) and baseline NLR with Pearson coefficient of 0.103 (P=0.03) and 0.394 (P<0.001) (*Table 2* and *Figure 1*). Nonetheless, SII was not found to be associated with baseline FACED score.

Sensitivity analysis

Sensitivity analysis was conducted with multivariate logistic regression adjusted by (I) adjusting factors that are significant in univariate logistic regression; (II) age, gender, smoking status and FACED score and; (III) age, gender, smoking status and BSI. They show consistent results which are summarized in Table S1.

Discussion

To our best knowledge, this is the first report on the role of SII in bronchiectasis in predicting the risks of hospitalized bronchiectasis exacerbation over 4.5 years of follow-up, as well as correlating SII with various markers of disease severity in bronchiectasis. Our findings suggested the

Table 2 Baseline SII level and correlation with other parameters of severity in bronchiectasis

Parameters	Pearson's correlation coefficient	P value
FEV_1 (L)	–0.190	0.001*
FEV_1 (% predicted)	–0.199	0.001*
FVC (L)	–0.073	0.22
FVC (% predicted)	–0.167	0.005*
Extent of bronchiectasis	0.103	0.03*
FACED score	0.001	0.99
E-FACED score	0.009	0.84
Bronchiectasis Severity Index	0.038	0.41
NLR	0.394	<0.001*

*, statistically significant. SII, systemic immune-inflammation index; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; FACED score, FEV_1, age, chronic colonization, extension, and dyspnea score; E-FACED score, exacerbation, FEV_1, age, chronic colonization, extension, and dyspnea score; NLR, neutrophil to lymphocyte ratio.

potential role of this simple and readily available marker in prognostication of bronchiectasis, especially on risks of hospitalized bronchiectasis exacerbation.

Bronchiectasis is a chronic airway disease with neutrophilic inflammation being the predominant pathophysiological mechanism. As such, different blood and sputum inflammatory markers have been studied. However, not all the markers are readily available with high costs being one of the potential hurdles for wide clinical use. While sputum cytokines can be measured, it needs fresh sputum specimens that are properly handled and stored. Special test kits are also required to perform sputum cytokine assays and the cost cannot be underestimated, not to mention the need for a dedicated machine and instrument, which is not available in all centres. For blood inflammatory markers such as C-reactive protein (CRP) and high-sensitivity C-reactive protein (hs-CRP), although they can be easily collected by blood sampling, the costs are still relatively high compared with complete blood count. One of the more readily available blood biomarkers that has been studied in bronchiectasis is NLR, which is calculated by dividing the number of neutrophils by the number of lymphocytes. There have been studies suggesting the role of NLR in bronchiectasis, mainly in prognostication (34).

While SII is similar to NLR, it also incorporates the baseline platelet count in its calculation. There were studies comparing SII and NLR. A study compared SII and NLR in predicting one-year survival in patients with untreated advanced hepatocellular carcinoma and the discriminatory ability based on area under receiving operator curve of SII was superior to that of NLR (35). The superior prognostic value of SII over NLR was also demonstrated in another study in lung cancer (36). In another study on hypertension, it was suggested that SII may be a superior systemic inflammation warning marker for hypertension (37). The incorporation of platelet count could potentially enhance the predictive value over NLR as thrombocytosis is one of the common responses to systemic inflammation. As such, SII could better reflect the degree of systemic inflammation over NLR.

As a readily available biomarker at low cost, the potential role of SII in exacerbation prediction, as well as correlating with disease severity is demonstrated in our study. SII can be easily calculated with neutrophil, lymphocyte, and platelet count from a peripheral blood complete blood count with a simple formula. It is easily repeatable and allows serial measurements. A Chinese study reported the reference intervals of SII among parameters in healthy controls to be between 142×10^9/L and 804×10^9/L (38). In the same study, gender and age were reported to be factors affecting SII value.

Our finding of the association between SII and risks of hospitalized bronchiectasis exacerbation can be explained by the underlying pathophysiology of bronchiectasis. Due to chronic systemic inflammation, elevated baseline platelet and neutrophil count with reduced lymphocyte count is expected to be seen in patients with bronchiectasis. This is more pronounced in patients with more severe bronchiectasis, as reflected by worse lung function parameters and more lung lobes being involved. As a disease characterized by neutrophilic inflammation, elevated baseline neutrophil count is expected in bronchiectasis. This phenomenon has been reported in previous literature as well. The elevated baseline platelet count is also explained by the same phenomenon. On the other hand, nutritional deprivation as a result of chronic inflammatory state can explain the reduced baseline lymphocyte count. By incorporating these three factors, SII can predict not only the bronchiectasis exacerbation risks, but also the disease severity, as reflected by spirometric values and extent of bronchiectasis.

We need to acknowledge the limitations of our study. First of all, this is a single centre study that only involved QMH. However, QMH is a tertiary referral medical centre in Hong

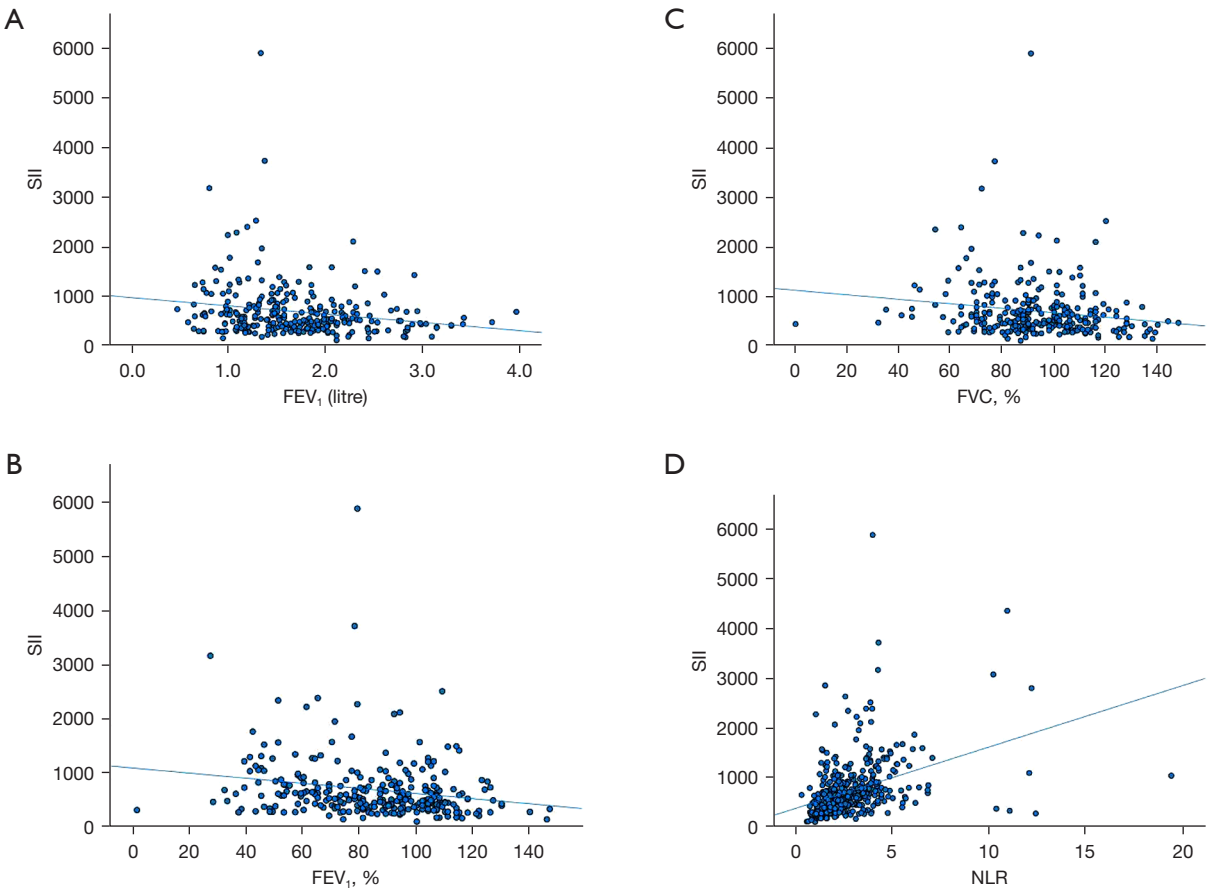

Figure 1 Scatter plots of the correlation between baseline SII and (A) FEV_1 in litre; (B) FEV_1 (percentage predicted); (C) FVC (percentage predicted); (D) NLR. SII, systemic immune-inflammation index; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; NLR, neutrophil to lymphocyte ratio.

Kong, as well as an affiliated hospital of The University of Hong Kong. The respiratory division of QMH received referrals from various healthcare facilities throughout Hong Kong, with a designated bronchiectasis specialty clinic for management of patients with bronchiectasis. Secondly, spirometry performed at different time points for the patients. Despite this limitation, the results from this study are consistent with previous reports in the literature. As this is a retrospective study, the timing of complete blood count was not standardized within the cohort. Nonetheless, the blood samples for complete blood count were taken at clinical stable-state well apart from exacerbation. While SII was shown to be able to predict bronchiectasis exacerbation risks, SII consisted of three components, namely neutrophil count, lymphocyte count and platelet count. However, lymphocyte count and platelet count were not statistically different between the two groups. It might mean the differences in bronchiectasis exacerbation risks could be mediated mainly by neutrophil count. Yet, a constellation of three different parameters within SII could still represent a more comprehensive assessment of the inflammatory status as shown in a previous study.

Conclusions

SII can serve as a biomarker to predict the risks of hospitalized exacerbation in patients with bronchiectasis, as well as correlate with the disease severity.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1392/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1392/coif). M.S.M.I. serves as an unpaid editorial board member of *Journal of Thoracic Disease*. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of the University of Hong Kong and Hospital Authority Hong Kong West Cluster (UW 20-435) and individual consent for this retrospective analysis was waived.

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