A Meta-Analysis of the Impact of Obesity, Metabolic Syndrome, Insulin Resistance, and Microbiome on the Diagnosis of Barrett’s Esophagus

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Keywords
Barrett’s esophagus · Abdominal obesity · Metabolic syndrome · Insulin resistance · Microbiome

Abstract
Background and Aim: The etiology and pathogenesis of Barrett’s esophagus (BE) have been widely studied during recent decades. However, the association between BE and possible risk factors, including abdominal obesity (AO), metabolic syndrome (MetS), insulin resistance (IR), and the microbiome has not reached a consensus and lacks a systematic assessment. The purpose of our study is to evaluate, quantify, and summarize the association between these factors and BE risk.

Methods: A systematic search of Pubmed, Embase, and Cochrane Library databases was performed to identify relevant studies before September 2018. Studies were estimated with the OR, the weighted mean difference (WMD), and the 95% CI by using a random effects model. Subgroup analysis and publication bias were also performed.

Results: A total of 46 citations were included in the analysis, and 119,273 subjects were analyzed (AO 13, MetS 15, IR 9, and microbiome: 9). The pooled results showed that AO (p < 0.01, OR 1.30, 95% CI 1.11–1.52, $I^2 = 31.9\%$), MetS (p < 0.01, OR 1.68, 95% CI 1.40–2.01, $I^2 = 87.6\%$), and IR (p < 0.01, WMD 0.23, 95% CI 0.11–0.35, $I^2 = 55.8\%$) were all significantly associated with an increased risk of BE, but except for the microbiome (p > 0.05, OR 1.27, 95% CI 0.66–2.43, $I^2 = 46.7\%$). In addition, subgroup analyses were stratified by waist-to-hip ratio, waist circumference, body mass index, diagnosis criteria, strain type, geographical region, and study design, respectively. Moreover, we observed no evidence of publication bias in Egger’s and Begg’s tests.

Conclusions: Our study reveals that AO, MetS, and IR are significantly associated with BE risk, except for the microbiome. The mechanism of BE induced by 3 risk factors should be further explored.

Introduction
Barrett’s esophagus (BE) has been defined as a pathological state that the stratified squamous epithelium of distal esophagus has been replaced by metaplastic columnar epithelium with goblet cells. BE has received significant attention because it predisposes patients to esophageal adenocarcinoma (EAC) of which prevalence has increased to more than 7 folds over the past several decades [1]. The overall prevalence of BE in Western countries ranges from 1 to 25% [2, 3], and the prevalence of histologically confirmed BE is 1.3% in Asia [4]. According to a recent epidemiological survey, the prevalence of BE is 1.6% in the general population [5]. Therefore, preventing BE based on risk factors will effectively reduce the preva-
lence of EAC. Estimates have suggested that BE are attributable to a large number of risk factors, such as chronic gastroesophageal reflux disease symptoms, advancing age, male gender, and tobacco use [6, 7]. In recent years, scholars have paid considerable attention to the association between BE risk and abdominal obesity (AO), metabolic syndrome (MetS), insulin resistance (IR), and the microbiome [8–13].

AO is a state of excessive abdominal fat around the stomach and abdomen, and is more likely associated with an increased risk of multiple chronic diseases, including diabetes, cardiovascular disease, and gastroesophageal cancer [14, 15]. Waist-to-hip ratio (WHR), waist circumference (WC), and body mass index (BMI) are main measures to categorize AO based on the value: WHR >0.90 for men, WHR >0.85 for women; WC >102 cm for men, WC >88 cm for women; BMI ≥30 kg/m² for men and women. MetS is a syndrome that contains more than three-fifths of medical conditions, including AO, high blood pressure, high blood sugar, high serum triglycerides, and low serum high-density lipoprotein. The diagnostic criteria for MetS mainly focus on the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) and the International Diabetes Federation (IDF) [16, 17]. IR is considered as a pathological condition in which cells fail to respond normally to the hormone insulin [18]. Homeostasis model assessment of IR (HOMA-IR) has been noted to be the most useful indicator for assessing an individual’s IR [19]. Many studies associated with IR are directly involved in glucose metabolism, and abnormal glucose has the ability to upregulate insulin-related signaling pathways in BE tissue [20]. Microbiome is the microorganism in the body and a part of the body. Recently, microbiome alterations have been implicated in the pathogenesis of inflammatory and neoplastic conditions in the gastrointestinal tract, especially in the esophagus [21]. Very recently, scholars have studied the alterations of the microbiome in BE, which mainly focused on Campylobacter, Proteobacteria, Firmicutes, Streptococcus, Bacteroidetes, and Actinobacteria [22, 23].

The association between BE and possible risk factors, including AO, MetS, IR, and the microbiome, has not reached a consensus and lacks systematic assessments. Some studies report that AO, MetS, IR, and the microbiome are supposed to be risk factors for BE [24–28]. However, the opponents point out that the association is generally originated from single-center studies which lack the sample size required for sufficient precision of statistical associations between risk factors and BE, and they have a dispute about risk factors associated with the development of BE [29, 30].

The main aim of this meta-analysis is to evaluate, quantify, and summarize the association between BE and AO, MetS, IR, and the microbiome by the subgroup analysis of WHR, WC, BMI, diagnosis criteria, strain type, geographical region, and study design where possible.

Methods

Search Strategy

Pubmed, Embase, and Cochrane Library databases were searched to identify relevant studies until September 2018. Search terms included a combination of “AO” or “central adiposity” or “visceral obesity,” “metabolic disease” or “MetS,” “IR” or “insulin sensitivity,” “microbiome” or “microbial” and “BE” or “Barrett esophagus” or “BE.” Cited studies and references of relevant studies were performed manually to search for additional studies.

Selection Criteria

Studies were included when the following criteria were fulfilled: (1) Case-control and cohort studies were chosen to assess the association between BE and 4 factors: AO, MetS, IR and microbiome; (2) Accurate definition of BE with histological evidence; (3) Well-defined AO estimated by (BMI, kg/m²), homeostasis model of assessment for IR (HOMA-IR) was calculated according to the standard formula (plasma glucose [mmol/L] × serum insulin [mLU/L])/22.5, and clear diagnosis of MetS was reported; (4) Studies reported OR and weighted mean difference (WMD) with 95% CI; (5) Studies (not case reports or meta-analyses) including estimation risk and initial data.

Data Extraction and Quality Assessment

Two independent investigators extracted the data from relevant studies while a third investigator resolved the discrepancy and reached a consensus. Data of risk factors in studies were extracted as follows: reference, year, country, study design, sample size, gender, mean age, mean BMI, MetS criteria, MetS prevalence, insulin, HOMA-IR, strain type, OR, and WMD with 95% CI. The methodological quality of primary studies was evaluated by the Newcastle-Ottawa Quality Assessment Scale. Bias analysis was necessary and studies with giant bias should be excluded.

Statistical Analysis

The software Stata 12.0 was applied to analyze the initial data. The data in this study was calculated as follows: (1) OR and WMD for binary and continuous data were abstracted, respectively. (2) Cochran’s Q test and I² index were used to assess heterogeneity. I² values of <30%, 30–59%, 60–75%, and ≥75% were assumed to represent low, moderate, substantial, and considerable heterogeneity, respectively. (3) Subgroup analyses according to BMI classification, diagnostic criteria of MetS, geographical region, study design, and strain type were performed. (4) Sensitivity analysis was conducted and publication bias was estimated by Begg’s and Egger’s tests.

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Results

Forty-six studies were included in the meta-analysis (Fig. 1).

Association Between AO and BE Risk

The association between AO and BE risk was assessed by 13 studies which reported characteristics of study samples: country, study design, sex composition, age, WHR (men > 0.90 and women > 0.85), WC (men > 102 cm and women > 88 cm), and BMI (< 25 kg/m$^2$, 25 kg/m$^2$ ≤ BMI < 30 kg/m$^2$, and ≥30 kg/m$^2$). The mean age of study samples ranged from 53.63 to 66.40 years old, and all sample populations were included in both men and women, except that one study was made up of a purely male population (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000502376).

The overall effect revealed that AO significantly increased BE risk (OR 1.30, 95% CI 1.11–1.52, Fig. 2a). Subgroup analysis was stratified by WHR, WC, BMI classification, geographic region, and study design. For subgroup analysis of WHR, the data of 4 citations showed a significantly increased risk of BE (OR 1.67, 95% CI 1.35–2.07), of which was larger than 0.90 for men and 0.85 for women, while the rest of the citations were not available (Fig. 2b). Since the data of WHR were not sufficient, we compared the effect of WC on BE risk. BE risks of WC subgroups (men > 102 cm and women > 88 cm; men < 102 cm and women < 88 cm) were 1.35 (95% CI 1.06–1.71) and 1.22 (95% CI 0.55–2.74) times higher than the normal population, respectively (Fig. 2c). BE risks of populations whose BMI ≥30 kg/m$^2$ (OR 1.29, 95% CI 1.04–1.59) and 25 kg/m$^2$ ≤ BMI < 30 kg/m$^2$ (OR 1.27, 95% CI 0.95–1.72) were slightly stronger than that of BMI < 25 kg/m$^2$ (OR 1.20, 95% CI 0.55–2.61, Fig. 2d). The increased risks were almost averagely distributed among the populations in world’s continents: European population (OR 1.22, 95% CI 0.83–1.78), North American population (OR 1.23, 95% CI 1.01–1.50), Asian population (OR 1.22, 95% CI 0.55–2.74, Fig. 2e). Comparing case-control studies with cohort studies, a 1.5-fold increased BE risk was observed (OR 1.38, 95% CI 1.17–1.62, Fig. 2f). Moderate heterogeneity was present in all analyses ($I^2 = 31.9\%$), and there was no evidence of public bias ($P_{\text{Begg's}} = 0.86, P_{\text{Egger's}} = 0.93$, online suppl. Fig. 1). In the sensitivity analysis, there was no significant variation of associations by excluding one study in each turn.

Association Between MetS and BE Risk

MetS and BE risk was assessed by 15 studies with characteristics: country, study design, sample size, sex composition, age, prevalence, and diagnosis criteria which
could be classified into 4 categories (IDF, NCEP ATP III, both of IDF and NCEP ATP III, neither IDF nor NCEP ATP III). The average age of populations in studies ranged from 45.00 to 76.60 years old, and the prevalence of BE fluctuated between 0.87 and 64.51% (online suppl. Table 2).

MetS was associated with a significantly increased BE risk (OR 1.68, 95% CI 1.40–2.01, Fig. 3a) with a considerable heterogeneity ($I^2 = 87.6\%$). In the subgroup analysis of diagnosis criteria, the criterion of neither NCEP ATP III nor IDF brought a significantly elevated BE risk (OR 4.94, 95% CI 1.71–14.28) which was the highest among other diagnosis criteria, and BE risk in the criterion of IDF (OR 1.81, 95% CI 1.60–2.05) was higher than that of NCEP ATP III (OR 1.36, 95% CI 1.14–1.63). However, the criterion of both NCEP ATP III and IDF had taken the lowest BE risk (OR 0.94, 95% CI 0.28–3.13, Fig. 3b). For subgroup analysis of geographic regions, European population had the highest BE risk (OR 2.35, 95% CI 1.39–3.98) compared to Asia population (OR 1.75, 95% CI 1.58–1.94), while North American population carried the lowest BE risk (OR 1.42, 95% CI 1.07–

**Fig. 2.** Forest plot for the association between AO and BE risk. **a** AO was significantly associated with BE ($p < 0.01$). **b–f** Subgroup analyses were stratified by WHR, WC, BMI classification, geographic region, and study design. AO, abdominal obesity; BE, Barrett’s esophagus; WHR, waist-to-hip ratio; WC, waist circumference; BMI, body mass index; NA, not available.

(Figure continued on next pages.)
The Relationship between BE and 4 Risk Factors

1.89, Fig. 3c). In study design analysis, case-control studies revealed a slightly higher risk than (OR 1.75, 95% CI 1.41–2.17) cohort studies (OR 1.46, 95% CI 0.89–2.39, Fig. 3d). Sensitivity analysis showed that the association was not driven by removing Drahos et al. [31]. No significant publication biases were detected by Egger’s and Begg’s test (P Begg’s  = 0.55, P Egger’s  = 0.14, online suppl. Fig. 2).

Association Between IR and BE Risk

IR with the association of BE risk was assessed by 9 studies, and we could observe the characteristics of study samples: country, study design, sample size, sex composition, age, insulin level, and HOMA-IR. The mean age of study samples ranged from 45.20 to 63.70 years old, and HOMA-IR was from 1.40 to 2.78 (online suppl. Table 3).
Our results indicated that IR was significantly associated with BE risk (WMD 0.23, 95% CI 0.11–0.35, Fig. 4a). There was moderate heterogeneity ($I^2 = 55.8\%$). The subgroup analysis of geographic region demonstrated that an increased BE risk was found in the European population (WMD 0.25, 95% CI –0.12 to 0.63) and Asian population (WMD 0.30, 95% CI 0.14–0.46) which was a 2-fold risk compared with the North American population (WMD 0.15, 95% CI –0.02 to 0.31). However, the Oceanian population showed an opposite association with BE risk, we blamed it on only one case of study (Fig. 4b). For study design, case-control studies were slightly associated with BE risk (WMD 0.27, 95% CI 0.20–0.35), but cohort studies (WMD –0.00, 95% CI –0.36 to 0.36) did not show any promotion on BE risk (Fig. 4c). Sensitivity analysis showed no significant variations in the association of BE risk.
The Relationship between BE and 4 Risk Factors

There were no significant publication biases in Egger’s and Begg’s test ($P_{\text{Begg’s}} = 0.12$, $P_{\text{Egger’s}} = 0.41$, online suppl. Fig. 3).

**Association Between Microbiome and BE Risk**

The association between microbiome and BE risk was analyzed by 9 studies, and we summarized the characteristics of study samples: country, study design, sample size, sex composition, and age. Besides, there was a variety of strain types in the study samples, such as *Proteobacteria*, *Campylobacter*, *Firmicutes*, and *Streptococcus*.

Our results revealed that microbiome was not associated with BE risk ($p = 0.48$, Fig. 5a) with a moderate heterogeneity ($I^2 = 46.7\%$). However, in the subgroup analy-
sis of strain type, *Campylobacter* showed a significantly increased risk for BE (OR 4.55, 95% CI 1.73–11.95), which was 4.6 times higher than that of the healthy population. *Proteobacteria* was not related to BE risk, and other strains, such as *Enterobacteriaceae*, *Firmicutes*, and *Streptococcus*, did not reflect the risk for BE (Fig. 5b). For the subgroup analysis of study design, cohort studies showed an increased risk for BE (OR 2.17, 95% CI 0.83–5.68), while case-control studies did not present an association (OR 0.88, 95% CI 0.38–2.02, Fig. 5c). In the sensitivity analysis, we did not observe an obvious alteration in the association of BE risk. There were no publication biases in Egger’s and Begg’s tests ($P_{\text{Begg's}} = 0.47$, $P_{\text{Egger's}} = 0.72$). online suppl. Fig. 4).
The Relationship between BE and 4 Risk Factors

**Fig. 4.** Forest plot for the association between IR and BE risk. **a** IR was significantly associated with BE \((p < 0.01)\). **b**, **c** Subgroup analyses were stratified by geographic region and study design. IR, insulin resistance; BE, Barrett’s esophagus.

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (95% CI)</th>
<th>Weight, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caro, 2015</td>
<td>0.33 (0.15, 0.51)</td>
<td>16.60</td>
</tr>
<tr>
<td>Greer, 2012</td>
<td>0.21 (-0.01, 0.44)</td>
<td>13.96</td>
</tr>
<tr>
<td>Hsu, 2011</td>
<td>0.41 (0.22, 0.60)</td>
<td>16.05</td>
</tr>
<tr>
<td>Ryan, 2008</td>
<td>0.58 (0.18, 0.98)</td>
<td>6.86</td>
</tr>
<tr>
<td>Winzer, 2015</td>
<td>-0.52 (-1.22, 0.17)</td>
<td>2.75</td>
</tr>
<tr>
<td>Arcidiacono, 2017</td>
<td>-0.29 (-0.82, 0.24)</td>
<td>4.41</td>
</tr>
<tr>
<td>Chak, 2015</td>
<td>-0.23 (-0.97, 0.50)</td>
<td>2.49</td>
</tr>
<tr>
<td>Duggan, 2013</td>
<td>0.10 (-0.16, 0.36)</td>
<td>12.11</td>
</tr>
<tr>
<td>Park, 2008</td>
<td>0.24 (0.18, 0.30)</td>
<td>24.78</td>
</tr>
<tr>
<td>Overall ((I^2 = 55.8%, p = 0.020))</td>
<td>0.23 (0.11, 0.35)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

**Study**

- **European population**
  - Caro, 2015: 0.33 (0.15, 0.51), 16.60
  - Ryan, 2008: 0.58 (0.18, 0.98), 6.86
  - Arcidiacono, 2017: -0.29 (-0.82, 0.24), 4.41
  - Subtotal \((I^2 = 70.3\%, p = 0.034)\): 0.25 (-0.12, 0.63), 27.87

- **North America population**
  - Greer, 2012: 0.21 (-0.01, 0.44), 13.96
  - Chak, 2015: -0.23 (-0.97, 0.50), 2.49
  - Duggan, 2013: 0.10 (-0.16, 0.36), 12.11
  - Subtotal \((I^2 = 0.0\%, p = 0.468)\): 0.15 (-0.02, 0.31), 28.56

- **Asian population**
  - Hsu, 2011: 0.41 (0.22, 0.60), 16.05
  - Park, 2008: 0.24 (0.18, 0.30), 24.78
  - Subtotal \((I^2 = 65.7\%, p = 0.088)\): 0.23 (0.11, 0.35), 40.83

- **Oceanian population**
  - Winzer, 2015: -0.52 (-1.22, 0.17), 2.75

**Study**

- **Case-control study**
  - Caro, 2015: 0.33 (0.15, 0.51), 16.60
  - Greer, 2012: 0.21 (-0.01, 0.44), 13.96
  - Hsu, 2011: 0.41 (0.22, 0.60), 16.05
  - Park, 2008: 0.24 (0.18, 0.30), 24.78
  - Subtotal \((I^2 = 18.7\%, p = 0.020)\): 0.27 (0.20, 0.35), 71.39

- **Cohort study**
  - Ryan, 2008: 0.58 (0.18, 0.98), 6.86
  - Winzer, 2015: -0.52 (-1.22, 0.17), 2.75
  - Arcidiacono, 2017: -0.29 (-0.82, 0.24), 4.41
  - Chak, 2015: -0.23 (-0.97, 0.50), 2.49
  - Duggan, 2013: 0.10 (-0.16, 0.36), 12.11
  - Subtotal \((I^2 = 65.2\%, p = 0.021)\): -0.00 (-0.36, 0.36), 28.61
**Fig. 5.** Forest plot for the association between the microbiome and BE risk. **a** The microbiome was not associated with BE ($p > 0.05$). **b, c** Subgroup analyses were stratified by strain type and study design. BE, Barrett’s esophagus.
Discussion

In this systematic analysis of 46 studies reporting on 119,273 subjects, we make sure that AO, MetS, and IR are all significantly associated with BE.

AO: Recent studies have shown that AO measured by WHR and WC, which are better than BMI, is involved in the progression to BE and EAC [10, 32, 33]. The WHO states that WHR which belongs to AO is above 0.90 for males and above 0.85 for females, respectively [34]. For subgroup analysis of WHR, the data extracted from the available citations were all significantly higher than that of the WHO standard. The results indicated that AO measured by WHR which was greater than the WHO standard was a key factor for the risk of BE. Due to insufficient data of WHR, we also performed the subgroup analysis of WC as a supplementary explanation. AO is determined as WC of above 102 cm for men and above 88 cm for women [35]. The WC of the obese population showed a higher risk of BE than that of a healthy population, which was consistent with other studies [36, 37]. Interestingly, we observed that the WC of the healthy population also had 1.22 times of BE risk, while we originally supposed that the healthy population with normal WC were not easy to suffer from BE. We attributed the opposite conclusion to a few citations (only 2 citations). In addition to WHR and WC, BMI is also used to measure AO. Subgroup analysis stratified by BMI classification revealed that obese population (BMI ≥30 kg/m²) and overweight/pre-obese population (25 kg/m² ≤ BMI <30 kg/m²) had a higher BE risk than underweight or healthy people (BMI <25 kg/m²), the results were similar to other studies [8, 29]. According to the subgroup analysis of the geographical region, European, North American, and Asian populations were proved to have same risks of BE, but Oceanian populations were more likely to suffer from BE than other populations, we blamed the reason to the insufficient number of study. The result was significant in case-control studies, but not in cohort studies. It might originate from a random error, so it was necessary to include more studies in cohort studies.

MetS: MetS includes a series of metabolic disorders, such as the large waistline, high triglyceride, low levels of high-density lipoprotein cholesterol, high blood pressure, and elevated levels of fasting blood sugar. It has been considered as a risk factor for gastrointestinal diseases such as gastroesophageal reflux disease and BE [38–40]. Similarly, our results proved that MetS was an important contributor to BE, but the heterogeneity was considerable. We speculated that the heterogeneity was derived from the included citations, especially from the citations Cook 2016 and Duggan 2013, because the ORs of these 2 citations were almost inconsistent with others. In addition, our subgroup analysis of diagnosis criteria (NCEP ATP III and IDF) demonstrated that the neither-subgroup and the both-subgroup showed the considerable heterogeneity due to containing the citations Cook 2016 and Duggan 2013, although NCEP ATP III and IDF themselves might not be one of the sources of the heterogeneity. The subgroup analyses of the geographical region and study design also revealed that the considerable heterogeneity in the North American population and study designs are derived from Cook 2016 to Duggan 2013. Apart from these 2 citations, the result of the sensitivity analysis did not show significant variations in the association of BE risk by removing Drahos 2016, which demonstrated that Drahos 2016 was not the resource of the considerable heterogeneity.

IR: IR is defined as the inability of a quantity of exogenous or endogenous insulin to increase glucose uptake and utilization in a normal population [41]. Some scholars have confirmed the association between IR and BE [42, 43]. In addition, patients with BE are more likely to develop EAC with higher levels of leptin and IR [44]. As stated above, our studies also confirmed that IR was associated with BE. In the subgroup analysis based on geographical regions, BE risk was significant in Asian, North American, and European populations, but except for Oceania population. Only one observational study was conducted in Oceania population [45], which might limit the accuracy of the pooled estimates. The association between IR and BE risk appeared only in case-control studies, but cohort studies did not show any evidence that IR was a risk factor for BE.

Microbiome: Microbiome is a rapidly advancing research topic in BE and EAC [46–48]. Some researchers believe that microbiome is a key factor in the pathological process of BE, while others hold the opposite opinion [48, 49]. Our results revealed that the microbiome did not have a significant association with BE risk, but had a tendency to become a risk factor for BE. Although the overall result was negative, we observed a positive result by the subgroup analysis of strain types. Microbiome alterations were mainly concentrated in Campylobacter and Proteobacteria, and Campylobacter was significantly associated with the risk of BE, while Proteobacteria might not be related to BE risk. Based on the negative results, we speculated that this association would be more accurate with more citations. Additionally, the overall negative results with subgroup positive
results indicated that individualized analysis of esophageal microbiome was an inevitable step in the diagnosis of BE.

Our study reveals that AO, MetS, and IR are significantly associated with BE risk, except for microbiome. These risk factors should be seriously considered when diagnosing and preventing BE and associated adenocarcinoma in clinical practice. However, it is still unclear how these factors induce metaplastic transformation in the human esophageal epithelium, which should be further explored.

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**References**


**Statement of Ethics**

Approval for the publication of this meta-analysis has been obtained from the Ethics Committee of Xi’an Jiaotong University (Certificate No. 2018-1034). All the procedures in the study involving human material and data were performed in accordance with World Medical Association’s Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subject.

**Disclosure Statement**

The authors have no conflict of interest.

**Author Contributions**

Y.C. designed experiments; J.D. carried out experiments and analyzed experimental results; D.C. and Y.L. collected experimental data; J.D. wrote the manuscript.
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