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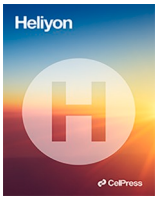

Review article

Reasons why women are more likely to develop primary biliary cholangitis

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ABSTRACT

Primary biliary cholangitis (PBC) is a chronic autoimmune disease of biliary stasis in which immune factors cause the gradual destruction of small bile ducts, biliary stasis, and eventually the development of liver fibrosis, cirrhosis, and even liver failure. One of the main characteristics of PBC is that it primarily affects middle-aged women, but the precise cause is still unknown. This article analyzes the unique causes and mechanisms of the female predominance of PBC and summarizes the potential causes.The female domination of PBC is reported to be primarily caused by sex hormones, environmental circumstances, and epigenetic changes, each of which has a different subtle impact on patients' gender disparities.

1. Introduction

Primary biliary cholangitis (PBC) is a classic autoimmune disease that targets the small intrahepatic bile ducts and causes histologic changes characterised by chronic nonsuppurative inflammation and granulomatous inflammation [1,2]. Anti-mitochondrial antibodies (AMA)—high titres of autoantibodies against the E2 subunit of the pyruvate dehydrogenase complex (PDC-E2)—are detected in the blood [3,4]. Bile duct loss, cholestasis, liver fibrosis, and even cirrhosis can result from an immune response that is persistent and damaging to the liver [5,6].

Like other autoimmune diseases, PBC has a typical sexual dimorphism, with a clear predominance of females and a female-to-male ratio that can be as high as 10:1. It mainly affects middle-aged women (40–60 years), and the changes in estrogen levels that occur after menopause make menopause and postmenopause the most common stages of PBC [7–9]. Research data suggest that worldwide, one in 1000 women over 40 years of age has PBC, and in many European and Asian countries, the prevalence and incidence are five and four times higher, respectively, in women than in men [10–12].To date, however, there is no definitive explanation for this apparent female preponderance, and the reasons for the high prevalence in women may be multiple, and an in-depth investigation may help us better understand why women are more susceptible.The purpose of this review is to provide an overview of women's greater susceptibility to PBC and to discuss the possible mechanisms behind it, based on the studies reported to date.

2. Sex hormones and endocrinology

Women are undoubtedly more susceptible to autoimmunity than men and are more likely to suffer from symptoms of pruritus and skin pigmentation in PBC, with pruritus occurring more frequently while taking oral contraceptives and during.pregnancy [13,14].

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Abbreviations

PBC	Primary biliary cholangitis
AMA	Anti-mitochondrial antibodies
PDC-E2	E2 subunit of the pyruvate dehydrogenase complex
SLE	systemic lupus erythematosus
lncRNA	long noncoding RNA
2-OA	2-Octynoic acid
BSA	bovine serum albumin
IFN	Interferon
ARE	Adenosine uridylate-rich element
GWAS	Genome-wide association study
UTIs	Urinary tract infections
HLA	Human leukocyte antigen
E. coli	Escherichia coli
IFIT1	IFN type-1
AE2	Anion exchange protein 2
BEC	Bile duct epithelium
TNF-α	Tumour necrosis factor α
3′UTR	3′-untranslated region
InsP3R3	Type III inositol 1,4,5-triphosphate receptor
XCI	X chromosome inactivation
XIST	X-inactive specific transcript
TLR	Toll-like receptor
PBMC	Peripheral blood mononuclear cell

Clinical studies have also found that PBC patients are more likely to undergo hysterectomy for menstrual irregularities and that PBC patients are more likely to receive hormone replacement therapy [15,16]. All these evidences suggest that predominantly female PBC may be related to sex hormones.

Sex hormones affect the function of immune cells by binding to their receptors. In general, estrogens are thought to enhance humoral immunity, whereas androgens and progestins suppress it [17]. The ERS1 and ERS2 genes encode the nuclear estrogen receptors ERα and ERβ, respectively, which are differentially expressed in different tissues and cells, mainly ERα in T cells and ERβ in B cells, and can modulate the immune response through binding effects with ERα or ERβ [15,18].Binding of estrogen to ERα stimulates proliferation of Th17 cells, which affects a number of autoimmune diseases [19]; increased estrogen levels during pregnancy lead to decreased production of B lymphocytes through interaction with ERα or ERβ; In contrast, serum immunoglobulin levels were elevated in nonpregnant women following estrogen therapy; low doses of estrogen also induce production of pro-inflammatory cytokines by mononuclear macrophages [20].ERβ expression in T cells was significantly lower in patients with systemic lupus erythematosus (SLE) than in controls, as also observed in inflammatory bowel disease species [21,22].ERα was found to exhibit strong pro-inflammatory properties in which ERβ was found to inhibit immunoreactivity in SLE mice by SLE mouse model [23].

More importantly, estrogen has been shown to have an effect on bile duct cells and bile acids [24].It is well known that the accumulation of bile acids in the liver of patients with PBC activates an inflammatory response that leads to further liver damage. Li et al. showed that cholangiocytes secrete exosomes rich in the long noncoding RNA (lncRNA) H19 in cholestasis, and estrogen increases the release of H19 and exacerbates cholestatic liver injury [25]. In addition, estrogen induces proliferation of bile duct cells.

In conclusion, sex hormones are one of the reasons for female dominance of PBC(Table 1), and further studies will help us to better understand the mechanisms behind it.

Table 1
Effect of different sex hormones on autoimmune diseases.

Name of hormone	Role in autoimmune diseases
estrogen	Enhancement of humoral immunity [84] E2 inhibits Th1/Th17 cell initiation in inflammation [85] Promotes survival of autoreactive B cells and modulates susceptibility to autoantigens [86,87] E2 supplementation in postmenopausal women stimulates IFN production [88] Retards the degradation of IκB
androgen	Immunosuppression [84] Decreased secretion of IL-4, IL-5 and IFN-γ in mouse T cells [89]
prolactin	Pro-inflammatory factors [89]

3. Environmental factors

The pathogenesis of PBC is complex and has not yet been elucidated, but numerous studies have pointed to the importance of environmental factors in pathogenesis. This double whammy leads to the development of PBC when genetically susceptible individuals are exposed to a pathogenic environment, and we will then discuss the relevant environmental factors that may contribute to female dominance.

3.1. 2-Octynoic acid

2-Octynoic acid(2-OA) is a synthetic chemical that occurs in nature in extremely small amounts and is widely used in perfumes, lipsticks, nail polishes, hair dyes, and other cosmetic products for women [26–28].Its structure is very similar to the immunodominant epitope of PDC-E2, and when it invades as an exogenous substance, it can disrupt immune tolerance and heterologously modify PDC-E2 to generate immunogenic neoantigens with enhanced serological recognition in patients with AMA -positive PBC [29–31]. Several epidemiological studies have indicated that frequent use of nail polish and hair dye is associated with susceptibility to PBC, highlighting the role of this exogenous factor [32,33].

The role of 2-OA has also been further demonstrated in the PBC mouse model [34]. Immunisation of C57BL/6 mice with 2-OA in combination with bovine serum albumin (BSA) resulted in the pathological damage characteristic of PBC, manifested as autoimmune cholangitis, high titers of AMA, massive $CD8^+$ T-cell liver infiltration, and granulomatous inflammation [35,36]. These results are compelling and indicate the potential pathogenicity of 2-OA.

3.2. Interferon-γ

Recently, an IFN-γ-based design of the ARE $Del^{-/-}$ PBC mouse model was developed, prolonged and chronified IFNγ expression by deleting the adenosine uridylate-rich element (ARE) in the 3′-untranslated region of IFNγ [37,38].ARE $Del^{-/-}$ mice not only exhibit the pathological features of PBC, but also have a significant sex-specific variation, with females exhibiting greater lymphocyte infiltration, bile duct destruction, granuloma formation, and greater AMA circulation compared to males, and estrogen enhancing lymphocyte activity and promoting greater IFN-γ production [39].The gene IRF5, which regulates IFN-γ expression, has been identified as a risk susceptibility gene for PBC in genome-wide association study(GWAS), and in vitro estrogen treatment leads to upregulation of IRF5 expression [40,41].

This is the first predominantly female mouse model of PBC that has attracted much attention and has led to consideration of the relationship between IFN-γ and sex variation in PBC. In PBC, as in other autoimmune diseases, there is overexpression of interferon in females, and chronic interferon stimulation can activate autoimmunity and lead to immune dysfunction.

4. Microbiology

The gut microbiota also plays an important role in the development of PBC, Huang et al. conducted a study of the gut microbiota in patients with PBC, and the results showed that the gut microbial abundance and population composition of patients carrying the high-risk allele were significantly lower compared to patients with PBC who did not carry the high-risk allele of HLA-DRB1 [42].An increased number of *Veillonella*, which has been reported to be associated with urinary tract infections(UTIs), was also found in PBC patients carrying human leukocyte antigen (HLA) susceptibility genes [43].

Large-scale epidemiological and case-control studies have found that patients with PBC are more likely to have bacteriuria and a higher incidence of UTIs compared with control subjects [44,45]. In an investigation of risk factors in patients with PBC, it was found that the OR for the presence of vaginal or urinary tract infections was elevated only in women compared to patients with other autoimmune diseases or the non-PBC population, with statistically significant results [46].One cannot help but associate bacterial infections with the risk of PBC disease, especially for female patients,and *Escherichia coli* (*E. coli*) has been cited as a common pathogenic microorganism in studies. Bacterial infections and exogenous exposure can lead to loss of immune tolerance and subsequent autoimmunity, with molecular mimicry being a key mechanism for the induction of PBC pathogenesis [47,48].Studies have shown that *E. coli* PDC-E2 is significantly homologous to human PDC-E2 and has a similar sequence of lipid acyl structural domains [29,49]. PDC-E2, as an autoantigen, is a major target of PBC attack and is located on the inner mitochondrial membrane.Through microbial mimicry, PDC-E2 is presented to T cells and stimulates the production of AMA, which increases the risk of disease in PBC [50]. Moreover, human and *E. coli* PDC-E2 share the entire ExDK sequence, which is required for recognition by $CD4^+$ T cells [27].

In addition to *E. coli*, *Lactobacillus delbrueckii*, a normal vaginal commensal, is also pathogenic. *Lactobacillus delbrueckii* shares a common motif with PDC-E2, and altered vaginal flora and recurrent vaginitis can lead to urinary tract infections [26]. *E. coli* can also cause vaginal infections [27].

Due to their specific physiology, women are more prone to urethral and vaginal infections than in a microbial environment, suggesting that bacterial infections may also be one of the environmental factors contributing to PBC prevalent in women.

5. Genetics and epigenetics

In addition to environmental factors, PBC has a strong genetic susceptibility.Epidemiologic mediation showed that patients with a positive family history accounted for 1.3%–9%, and the prevalence of first-degree relatives of patients with PBC was higher, and it was

found that first-degree relatives of patients with PBC presented with AMA at a greatly increased frequency, even 100 times higher than that of the healthy population, with a clear family aggregation [51,52].Compared to dizygotic twins, the prevalence of PBC in monozygotic twins is as high as 63%, which is a high level among autoimmune diseases [53].Thanks to the GWAS for PBC over the last decade or so, important support has been provided for the genetic susceptibility of PBC.Seven large GWAS analyses to date have identified HLAII as the strongest risk locus for PBC, encompassing more than 70 PBC susceptibility loci, as well as many non-HLA loci [54].

Between environmental and genetic factors, we have to discuss the influence of epigenetics on PBC,Although research on the epigenetics of PBC started late, it nonetheless provides data that can be used for reference.Epigenetic studies of the X chromosome may better explain female dominance in PBC, in addition to methylation, histone modifications, and noncoding RNAs, which are also involved in the pathogenicity link, we will discuss each of them next.

5.1. Methylation

In a cohort study of three pairs of identical twins screened for methylation profiles, 60 genes were found to have methylation differences compared to unaffected twins, 51 of which were located on the X chromosome, these genes cause downregulation of IFN type-1(IFIT1) signaling, suggests that women may be more susceptible to PBC [55].Lleo et al. analysed the DNA methylation profiles of CD4+T, CD8+T, and $CD14^+$ T cells on the X chromosome in 30 female PBC patients and 30 age-matched controls and showed that the promoters of CD4+T, CD8+T, and $CD14^+$ T cells in PBC patients had 20, 15, and 19 different DNA methylation patterns, respectively [56].In particular, Hypermethylation of FUNDC2 involved in mitochondrial autophagy in $CD8^+$ T cells, CXCR3 is significantly demethylated in $CD4^+$ T cells, leading to upregulation of CXCR3 expression, and the persistent presence of CXCR3 recruits more cells to infiltrate, promoting disease progression [57,58].

CD40L is also a known X-linked gene, and studies have shown that DNA methylation of the CD40L promoter is reduced in $CD4^+$ T cells from PBC patients and negatively correlates with serum IgM levels in PBC patients [59]. CD40L plays an essential role in T cell initiation and B cell maturation, and the interaction between CD40 and CD40L affects IgM production, and elevated serum IgM levels in PBC patients are common clinical abnormalities in biochemical indicators [60].

The above methylation changes associated with the X chromosome affect the disease process of PBC in different ways, highlighting the important role of epigenetics in predominantly female PBC.

5.2. Histone modification

Currently there are not many studies on PBC histone modification, it is worth noting that some studies have shown that β-arrestin 1 expression is elevated in T lymphocytes from PBC patients, and β-arrestin 1 overexpression promotes the acetylation of histone H4 in the promoter region of LIGHT, CD40L, IFN, and IL17, and at the same time makes TRAIL, APO2, and HDAC7A promoter region histone H4 deacetylation to regulate T cell proliferation and activation, and produce large amounts of IFN, β-arrestin 1 gene expression level and PBC severity were positively correlated [61].

The role of histone modifications in PBC and even other autoimmune diseases should not be underestimated, and in the future we need more studies to elucidate the genetic markers and epigenetic fine-tuning of histone modifications.

5.3. MicroRNA506

Under normal physiological conditions, ductally secreted $HCO3^-$ is secreted via $Cl^-/HCO3^-$ anion exchange protein 2 (AE2), which is located at the tip of the bile duct epithelium (BEC) and covers the surface of the BEC to form a bicarbonate screen that protects PH homeostasis from hydrophobic toxic bile acids [62,63].Several pro-inflammatory cytokines such as interleukins and tumour necrosis factor α (TNF-α), which are highly expressed in the liver of PBC patients, can trigger the activity of miR-506 to enhance their expression [64].Up-regulated miR-506 binds to the 3′-untranslated region (3′UTR) of AE2 mRNA, thereby preventing protein translation, leading to downregulation of AE2 expression when decreased AE2 activity results in PH dysregulation, which allows uncontrolled entry of toxic bile acids into the BEC, resulting in bile sludge and promoting apoptosis and immune activation [65,66].Since endo-lysosomal milieu is more acidic in females than in males, reduced AE2 activity is more likely to affect mitochondrial function in females, and impaired mitochondrial autophagy leads to oxidative stress, PDC-E2 overexpression, and immune activation, which may contribute to our understanding of why females are more susceptible to PBC in light of impaired mitochondrial autophagy [67].

In addition to AE2, miR-506 negatively regulates the Type III inositol 1,4,5-triphosphate receptor(InsP3R3), an important component of the BEC endoplasmic reticulum that functions as a $Ca2^+$ regulator and also promotes bile bicarbonate secretion [68,69]. Thus, miR-506 downregulates both AE2 and InsP3R3 activity, promotes BEC apoptosis leading to overexpression of PDC-E2, while causing mitochondrial metabolic damage and promoting oxidative stress [64]. Moreover, studies have shown that overexpression of miR-506 leads to upregulation of pro-inflammatory, pro-fibrotic and senescence gene expression [30].

Interestingly, the protagonist of the above event, miR-506, is an X-linked gene located on Xq27.3, which may have contributed to the female dominance of PBC [5,69]. The X chromosome is rich in microRNAs and 7% of the identified microRNAs are encoded on the X chromosome, however further exploration of female-biased X-linked MicroRNAs is needed to broaden our understanding of the etiology of PBC.

5.4. X chromosome

In autoimmune diseases where there is a gender bias, investigation of the sex chromosomes is the most intuitive way for us to understand sex differences in disease.Five percent of the nuclear genome is the X chromosome, and mutations localized on it account for about 10% or so of Mendelian diseases, yet unfortunately there are fewer GWAS analyses of the X chromosome in PBC [70].

A recent genome-wide association study of the x-chromosome pointed to PBC susceptibility genes such as OTUD 5, TIMM17B, PQBP 1, KCND1, and that OTUD 5 as the most prominent site may be related to T cell function [71].

X-chromosome monosomy is the presence of only one chromosome in a homologous chromosome, and partial or complete loss of a single chromosome poses a disease risk and can be fatal [48].To investigate the reasons for female dominance in PBC, Invernezzi et al. performed fluorescence in situ hybridization to determine the abundance of X chromosome monomers in 100 female PBC patients and 50 healthy controls, and showed that X chromosome monomers increased with age in both groups and were significantly more abundant in female PBC patients than in controls [72,73].In addition, a higher abundance of X chromosome monomers was observed in T and B lymphocytes [74]. Although loss of X monosomes in somatic cells is random, reports indicate that loss of X monosomes appears to be preferential and heritable in PBC [24].

In contrast to X chromosome monosomy, X chromosome inactivation (XCI) is the random and permanent inactivation of one of the X chromosomes by XCI in female cells during embryonic development and can be used as a method to balance X-linked gene expression between female and male individuals [15].Variants have been identified in PBC for XCI, which is regulated by X-inactive specific transcript (XIST), a non-coding RNA located on the long arm of the X chromosome, LncRNA XIST is highly expressed in NK cells and $CD4^+$ T cells of PBC patients and may contribute to the predisposition of women to PBC by affecting the proliferation and differentiation of naïve $CD4^+$ T cells, and may further affect the production of IFN and IL-17.Elevated LncRNA XIST in PBC patients affects XCI, leading to escape of immune-related genes (e.g., CD40L, CXCR3) and increased cytokine secretion on the X chromosome, which affects Th1 and Th17 differentiation [75].DDX3X is the gene that evades silencing and mediates the production of type 1 IFN, which is clearly implicated in the pathogenesis of PBC, with high levels of DDX3X contributing to the upregulation of IFN in females compared to males [15].The toll-like receptor (TLR) 7 on myeloid and B cells in females activates type I interferon signaling by binding to single-stranded RNA; however, the X chromosome, which encodes TLR7, escapes XCI, which leads to an increased risk of PBC in females carrying two X chromosomes [76].

It appears that X chromosome-based alterations can intuitively explain predominantly female PBC, and that many genes on the X chromosome are regulated by methylation,the epigenetic studies of the unique X chromosome may provide a different perspective for understanding the underlying mechanisms of PBC.X-chromosome analysis is particularly important for autoimmune diseases in which there is a sex dominance, not only to help us find new loci, but also to shed light on the nature of sex differences in disease.

6. Gender and immunity

Gender differences create inconsistencies in the immune responses of males and females. Although males and females have the same types of immune cells in their bodies, their responses to microorganisms, viruses, and autoantigens are distinctly different.Females have stronger humoral and cellular immunity to these stimuli, so many infections are less common in females than in males, and

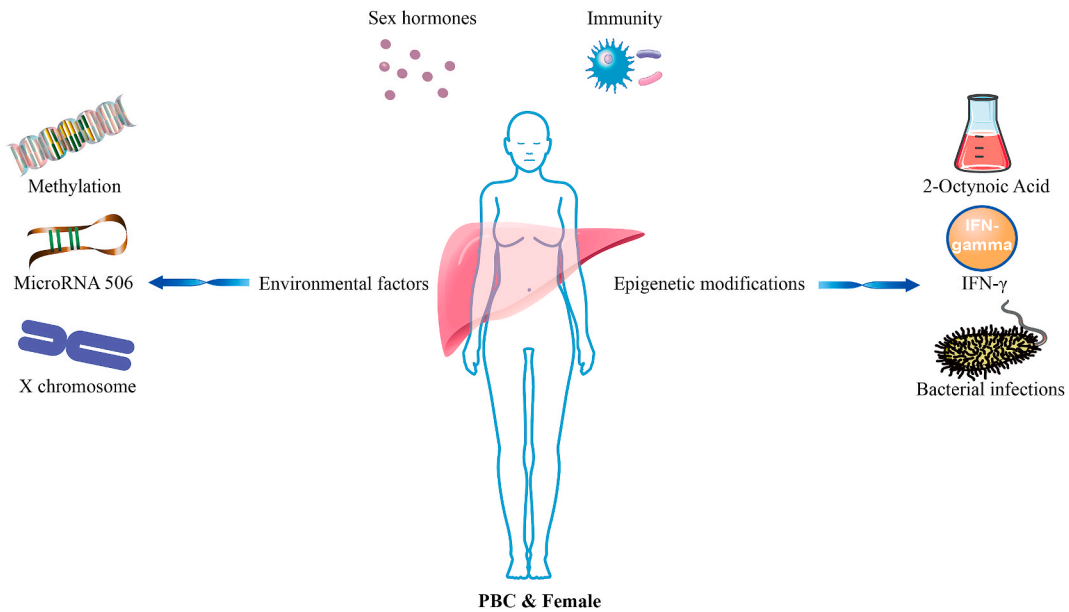

Fig. 1. Possible factors contributing to women's greater susceptibility to PBC.

females have stronger antiviral responses to vaccination than males [77].Although women show stronger innate and adaptive immunity, this also leads to a strong immune response to self-antigens, so women are more susceptible to autoimmune diseases [78].

This gender-borne immune difference is already present in the fetal period, with Barke et al. showing that the female placenta predominantly expresses TLR5 and the male placenta predominantly expresses TLR6 and TLR8, determining differences in susceptibility to infection [79].In addition, the expression of IFN-related genes in the female placenta is higher than that of males, and the immune response can also be regulated through gene imprinting, whereby gene imprinting from both parents drives or inhibits fetal growth while also regulating lymphocyte activation and differentiation and influencing the secretion of pro-inflammatory cytokines [80].It was also noted that in response to TLR7 stimulation, female Peripheral blood mononuclear cell(PBMC) produced more IFN-α and had a higher frequency of circulating $CD4^+$ T than males and produced more cytokines in response to infection than males [81,82].

Returning to PBC, we now understand that estrogen promotes IFN-γ production by Th1 cells, which regulates T-cell activation and differentiation, and animal models have shown that deletion of type I IFN signaling can alleviate PBC injury [83].Methylation profiling of peripheral blood from monozygotic twins with discordant PBCs pointed out that more than 80% of the differential genes are localized on the X chromosome, and that these genes play different roles affecting the immune function of T cells.miR-506 and poly I:C also influence immune activation in females.The role of the X chromosome, XCI, and the FOXP3 and CXCR3 genes localized to the X chromosome in influencing the immune system leading to the predisposition of females to PBC is even more self-evident.

7. Summary and future directions

In conclusion, PBC is a complex and dynamic progressive disease, and the reasons that contribute to women's predisposition to PBC are multifaceted, including genetic susceptibility, environmental triggers, and epigenetic modifications(Fig. 1).In addition to the genetic differences brought about by gender, hormones can also regulate the function of immune cells by binding to receptors and can bring about epigenetic changes.In the course of our research on this disease, we have often wondered why women are more susceptible to PBC. Deeper exploration of the underlying mechanisms will contribute to our understanding and also allow different clinical management of patients of different sexes, which may lead to a better prognosis for patients.In the future, it may be possible to study the genes associated with the X chromosome, which is the most intuitively and deeply linked to female susceptibility to PBC, and such loci as OTUD 5 and TIMM17B are worthy of in-depth investigation. In addition, the mitochondria should not be overlooked, as the autoantibodies specific for PBC are derived from the E2 subunit of the mitochondrial pyruvate dehydrogenase complex, and it is well known that mitochondria have a unique physiological function and typical maternal inheritance in females, which is inevitably associated with gender.More research is needed in the future to decipher the female dominance in PBC, bringing us new perspectives while advancing gender-personalized clinical care.

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Ethics statement

This article does not require an ethical statement as it is a review and does not involve ethical experimentation.

Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Di Ma: Writing – original draft. **Jiaxuan Ma:** Formal analysis. **Chunmei Zhao:** Data curation. **Wenlin Tai:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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