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## **A Quality-of-life Study in Patients with Anaphylaxis to Hymenoptera Venom in Iran**

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### **ABSTRACT**

Little is known about the quality of life of patients with anaphylaxis to Hymenoptera venom. The Vespid Allergy Quality of Life Questionnaire (VQLQ) is commonly used to assess the psychological burden of this condition. This study aimed to evaluate the validity and reliability of the Persian version of VQLQ.

In this cross-sectional study, VQLQ was translated into Persian according to expert recommendations. The final translated version of VQLQ was then administered to 115 patients with Hymenoptera venom allergy at an asthma and allergy clinic in Iran.

More than half of the participants were between 20 and 40 years of age, and 60% were male. Fear, anxiety, and outdoor activities had the most significant impact on the quality of life of patients with Hymenoptera venom allergy. Additionally, quality of life was more affected in women than in men, while no correlation was found with age. Furthermore, the quality of life was affected by a history of acute anaphylactic shock due to Hymenoptera venom.

The Persian version of VQLQ enables the measurement of quality of life in patients with Hymenoptera venom allergy in the Iranian population. The inclusion of VQLQ in the initial evaluation of these patients may potentially guide allergist in providing support for venom-specific immunotherapy.

**Keywords:** Allergy quality of life; Anaphylaxis; Hymenoptera; Hymenoptera venom; Quality of life

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## INTRODUCTION

Many studies have investigated the relationship between health-related quality of life (HRQoL) and the psychological burden of allergic illnesses.<sup>1</sup> Allergic diseases such as asthma,<sup>2</sup> allergic rhinitis,<sup>3</sup> and especially food allergies<sup>4</sup> have a significant impact on the overall quality of life of those affected by these conditions. Moreover, these diseases result in substantial direct and indirect costs, as well as intangible expenses, for the patients.<sup>5</sup> Self-reported results from patients are necessary for better evaluation of health status and the impact of new interventions.<sup>1</sup> Quality of life questionnaires are essential for evaluating health and treatment outcomes in daily clinical practice.<sup>6,7</sup> Hymenoptera venom allergy (HVA) is rare but potentially life-threatening.<sup>8</sup> The fear of an anaphylactic event after getting stung affects HRQoL significantly. Systemic allergic reactions to Hymenoptera venom occur in 0.3% to 7.5% of adults. The odds are less in children and more in beekeepers. However, significant local reactions at the bite site occur in up to 26% of the population.<sup>9,10</sup>

The most common causes of anaphylaxis are foods, medications, and insects. Anaphylaxis occurs in approximately 1% to 3% of people annually. In the United States, it occurs to 2% of the population at least once in a lifetime. The incidence of anaphylactic reactions is increasing, especially in women and younger individuals. Various studies have shown that the incidence of anaphylaxis is much higher than previously estimated.<sup>11</sup> According to registered anaphylaxis statistics in Europe, HVA is the leading cause of anaphylaxis in adults (48.2%), while it accounts for 20.2% of anaphylaxis episodes in pediatric patients.<sup>12</sup> Therefore, its impact on health, as well as emotional, social, and professional status of patients should not be underestimated.<sup>8,12</sup>

Epinephrine autoinjectors are a standard emergency tool used to reduce the immediate risk of death after a bee sting. However, it is difficult for the patient to continuously carry these autoinjectors.<sup>13,14</sup> The more worrying issue in this regard is the significant number of patients who have not received adequate training or do not have sufficient equipment.<sup>15</sup>

In contrast, venom-specific immunotherapy (VIT) is a therapeutic method that reduces the risk of an insidious

allergic reaction.<sup>16,17,18</sup> Even patients who receive VIT, regardless of years of immunotherapy, experience prolonged menace of a life-threatening systemic reaction.<sup>19</sup> This effect is related to the patient's awareness of the consequences and severity of the symptoms.<sup>12</sup> Studying HRQoL in these individuals helps identify the real impact of insect venom allergy based on reaction intensity, social relationships, mental health, fear, risk, and uncertainty.<sup>19</sup>

The Vespid Quality of Life Questionnaire (VQLQ), published in 2002, was the first tool to measure HRQoL in adult patients with wasp venom allergies.<sup>12</sup> VQLQ and its various versions consist of 14 questions, selected according to the impact methodology. In the questionnaire, each question is given a score from 1 to 7. Most of the questions focus on the patients' emotional aspects. There are also questions about the patient's job, leisure and outdoor activities. This questionnaire is valid for patients over 14 who have experienced a systemic reaction to Hymenoptera stings and is invalid for beekeepers due to their frequent exposure to bees. Furthermore, since it is considered an occupational disease in this population, the sufferers perceive their disorder differently.<sup>12,20</sup>

Based on the results of the content validity study of the VQLQ, the items can be classified into the 4 areas of anxiety, caution, limitations, and discomfort. However, the authors presented the VQLQ scale as a unidimensional measurement tool.<sup>12</sup> This easy and validated tool assesses impairment of HRQoL in patients with HVA, mainly due to emotional distress caused by feelings of anxiety associated with fear of being stung.<sup>12,21</sup> In addition, it was clinically shown that a significant improvement in HRQoL<sup>13</sup> and VQLQ scores<sup>22,23,24</sup> is possible with VIT.

The impact on HRQoL plays a key role for patients with allergy and anaphylaxis. Analysis of different studies indicates that several factors can adjust HRQoL in this group. These factors include sociodemographic data such as age and gender, and fear of accidental reactions. Moreover, external factors such as the social environment and perception of the seriousness of the situation by others can also impact HRQoL.<sup>25</sup>

A significant relationship between HRQoL and parameters of gender and treatment status has been observed.<sup>26</sup> In a study evaluating the effect of HVA in children and adolescents, it was concluded that there is a relationship between the sense of security perceived by

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parents and the stage of treatment and where they lived; the longer the immunotherapy period, the less anxious the parents were.<sup>27</sup>

There are methodological challenges in creating internationally or even cross-regionally comparable quality-of-life questionnaires. In addition to the language barrier, there are also significant cultural and ethnic factors that affect the perceived quality of life. Therefore, guidelines have been developed to reduce the consequence of this translation discrepancy between different languages in this regard.<sup>22</sup>

There are no questionnaires in Persian to evaluate the quality of patients' lives with a history of anaphylaxis after a bee sting. The main objective of this study was to construct a Persian version of VQLQ and to evaluate its utility in patients with HVA.

### MATERIALS AND METHODS

#### Cross-cultural Translation

The cross-cultural translation of VQLQ into Persian was performed, with the author's permission, by translating the original Dutch questionnaire, a forward and backward approach, and testing it on patients per published recommendations.<sup>13,21</sup> The procedure is described in Figure 1.

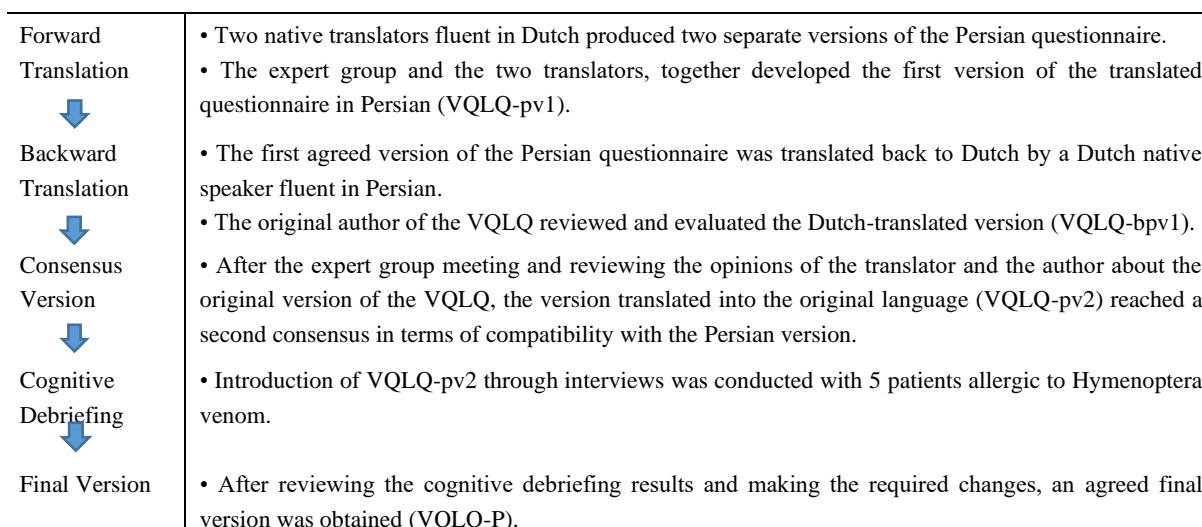
During the cognitive interview, the participants were instructed to provide feedback on the acceptability,

comprehensibility, and clarity of the questionnaire, and which was recorded by the investigators. After reviewing the results of the cognitive survey and combining the necessary modifications, the final Persian version of the questionnaire (VQLQ-P) was sent to the questionnaire was sent to an expert group with sufficient experiences in the field of asthma and allergy and was approved.

#### Participants and Study Design

Patients diagnosed with HVA between March 2008 and July 2022 at an asthma and allergy clinic (Dr. Bemanian Clinic) in Tehran were selected as participants. All Persian-literate patients with confirmed HVA (history of a systemic reaction to a Hymenoptera sting and a positive immunoglobulin [Ig] E or skin test) were included.

A structured survey included demographic data, reaction type, and the filled VQLQ-P. In addition to the information obtained in the study, all clinical records were reviewed and evaluated to confirm the diagnosis. A total of 115 individuals were included in the study. Each patient answered the questionnaire only once through phone call interviews. All the patients had the severe type of anaphylaxis, experienced a feeling of imminent death, experienced severe shortness of breath and suffocation, and were referred to the emergency medical services. The relationship between HRQoL and severe anaphylaxis in these patients was investigated by the validated VQLQ-P.



**Figure 1. Steps of translating the questionnaire from the original language to Persian.**

As the aim of this study was to evaluate HRQoL before VIT or autoinjection treatment, the questions inquired about the patient's quality of life before these treatments. Among the patients with HVA, 87 had received VIT, 22 patients were undergoing VIT, and 68 had received an autoinjection.

An epidemiologist oversaw all stages of the study, including the statistical calculations and validation in Persian.

### Instruments

VQLQ-P (Supplementary File 1) was used to measure HRQoL in individuals with HVA. VQLQ-P has 14 questions. The first 6 questions of this survey focus on different anxiety symptoms, including agitation, avoidance, and fear behaviors, such as running away, avoiding certain places, and need for control. The latter 8 questions evaluate stress due to increased vigilance. These are presented for general (e.g., being outdoors) and everyday situations (e.g., at work, while eating outside, gardening, being in nature, or on vacation). Most of the questions were about the emotional aspects of the patient's life, although questions about occupation, leisure time, and outside activities were also included).<sup>28,29</sup> Therefore, the first 6 questions of the questionnaire are about fear and anxiety. Questions 7, 10, and 12 are related to social activities, 8 and 9 are about outdoor activities, and questions 11, 13, and 14 are related to leisure and free time.<sup>12,21</sup>

In the questionnaire, the score of each question is ranked from 1 to 7 (1 being the highest and 7 the lowest quality-of-life score). Scores are summed and divided by the number of question items, except for the questions 10 to 14 with a "not applicable" option, which are not taken into account. Then, the total number of points will be counted and divided by 14. This arithmetic mean will be interpreted as the result of the questionnaire.

### Content Validity

An expert group of 7 specialists (5 Allergic diseases specialists and 2 specialists in designing and psychometric instruments) examined the initial questionnaire. The panel was asked to comment on individual items in relation to their accuracy, clarity, and style. Items were slightly modified based on expert reviews. Then, a separate panel of 10 allergic disease specialists was asked to comment independently on the

necessity and relevance of the items to calculate the content validity ratio (CVR) and content validity index (CVI), respectively.

The necessity of the items was assessed using a three-point rating scale as either not necessary, useful but not essential, or essential. Following the experts' assessments, a CVR for the total scale was computed. According to Lawshe, if more than half of the panelists determine that an item is essential, that item has at least content validity. The CVR in this study for the total scale was 0.62, showing a satisfactory result. The relevance of the items was also assessed using a four-point rating scale as either not relevant, slightly relevant, relevant, or very relevant. The CVI of each question is the proportion of experts who rate it as 3 or 4. Polite and Beck recommended a CVI of 0.80 as an acceptable lower limit.<sup>23</sup>

### Face Validity

The provisional scale was then administered to 5 individuals with HVA with different sociodemographic characteristics to assess the clarity and readability of the items. In general, there were no significant problems in reading or understanding the items.<sup>23</sup>

### Ethics

The study was approved by the ethics and clinical research committees of the participating clinic. All patients were informed about the study and provided their consent to participate. All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

### Statistical Analysis

All data analyses were performed using SPSS version 21.0 for Windows. Mean  $\pm$  standard deviation or median (minimum–maximum) for metric variables and frequency (percentage) for categorical variables were given as descriptive statistics. The Pearson or Spearman correlation coefficient was calculated to determine the association between variables, and ( $p < 0.05$ ) was considered statistically significant.

The reliability coefficient Cronbach's alpha was used to assess the internal consistency.<sup>24</sup> The internal consistency method was used to measure the reliability of the designed questionnaire. To measure internal consistency, a pilot study was conducted with the participation of 15 patients. Then, the study was repeated

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5 days later, and the results between the responses of the two studies were compared by the epidemiologist and calculated by a relevant Cronbach's alpha formula.

### RESULTS

#### Cross-cultural Translation of VQLQ-P

During translation, the closest match to the original version was preferred whenever comprehensibility was not affected. No questions or corrections were asked during the entire author approval phase. After achieving the approved version of the questionnaire, 5 participants were interviewed for further revision of the questionnaire. The surveyed participants did not report any problems or suggest any changes to the questionnaire.

#### Validation of the VQLQ-P

A satisfactory level of agreement was found

(CVI>0.79) among panelists, suggesting an acceptable content validity. The questionnaire validation results are shown in Table 1.

#### Internal Consistency of the VQLQ-P

The Cronbach's alpha of the 14 items was (>0.7) for 15 cases of those with confirmed HVA. The Internal consistency results are presented in Table 2.

#### Patient Population

The current study was conducted on 115 patients. Patients answered the questionnaire in approximately 10 to 15 minutes via phone call interviews. All patients had experienced a systemic reaction after a vespid and/or a bee sting. More than half of the participants were between 20 and 40, and 60% were men. The demographic characteristics are shown in Table 3.

Table 1. Content validation results of Vespid Allergy Quality of Life Questionnaire

Variable	Content Validity Ratio	Content Validity Index		
		Simplicity	Clarity	Relation
Fear and anxiety	0.95	0.92	0.90	0.85
Social activities	0.87	0.87	0.90	0.92
Outdoor activities	0.84	0.80	0.90	0.86
Leisure	0.90	0.86	0.93	0.96

Table 2. Internal consistency results

Questions	Cronbach's $\alpha$
Fear and anxiety	0.75
Social activities	0.73
Outdoor activities	0.79
Leisure	0.70

Table 3. Demographic characteristics of the studied population

Parameter	Participants, n (%)
Gender	Female 46 (40%)
	Male 69 (60%)
Age	Age < 20 7 (6.1%)
	20 < age < 40 54 (47%)
	40 < age < 60 52 (45.2%)
	60 < age < 80 2 (1.7%)
Total	115 (100%)

### VQLQ Outcomes

Descriptive results of the VQLQ questionnaire scores for different dimensions of the HRQoL, including mean, standard deviation, variance, median, minimum, and maximum, are presented in Table 4.

A higher score means a lower level of HRQoL, which was affected more in terms of fear, anxiety, and outdoor activities than other evaluated conditions.

According to the analysis of VQLQ scores, there were significant correlations between all the different dimensions of HRQoL (Table 5).

Questionnaire scores were analyzed in relation to age and sex. HRQoL was affected more in women compared to men ( $p < 0.01$ ), while no correlation was found with age (Table 6).

**Table 4. Descriptive results of the Vespil Allergy Quality of Life Questionnaire scores for different dimensions of quality of life.**

Score	Questions	Mean	Median	SD	Variance	Minimum	Maximum
Fear and anxiety	6	24.930	26.00	5.2944	28.030	11.00	36.00
Social activity	3	12.635	13.00	2.8077	7.883	6.00	19.00
Outdoor activities	2	8.322	9.00	2.3191	5.378	3.00	14.00
Leisure	3	12.965	13.00	2.9348	5.378	3.00	19.00
Quality of life (total)	14	58.852	60.00	10.0309	100.618	30.00	83.00

SD: standard deviation.

**Table 5. Pearson correlations between different dimensions of quality of life**

	Fear and anxiety	Social activities	Outdoor activities	Leisure	Quality of life (total)
Fear and anxiety	1	0.469**	0.335**	0.345**	0.838**
Social activities	0.469**	1	0.521**	0.502**	0.795**
Outdoor activities	0.335**	0.521**	1	0.201*	0.613**
Leisure	0.345**	0.502**	0.201*	1	0.662**
Quality of life (total)	0.838**	0.795**	0.613**	0.662**	1

\* $p = 0.031$  (2-tailed); \*\* $p < 0.0001$  (2-tailed).

**Table 6. Correlations between quality of life with age and gender**

		Quality of life (total)	Gender	Age
Quality of life (Total)	Pearson Correlation	1	0.348	0.083
	Sig. (2-tailed)		<0.0001	0.379
Gender	Pearson Correlation	0.348	1	-0.087
	Sig. (2-tailed)	<0.0001		0.354
Age	Pearson Correlation	0.083	-0.087	1
	Sig. (2-tailed)	0.379	0.354	

### DISCUSSION

In this research, a specialized quality of life questionnaire, VQLQ, was translated into Persian and validated for patients with HVA. The content and face validity of the questionnaire were checked by allergic diseases experts and patients suffering from anaphylactic shock due to Hymenoptera stings after several stages of translation and retranslation and matching the questionnaire with the original one.

VQLQ-P is the first version VQLQ translated into Persian, and appears to be a simple instrument for assessing HRQoL of patients with HVA. Nevertheless, a longitudinal evaluation of its usefulness is needed. The procedure of translation and cultural adaptation followed the recommendations of the Global Allergy and Asthma European Network (GA<sup>2</sup>LEN) guidelines.<sup>1</sup>

The original version of the VQLQ was initially developed in Dutch<sup>30</sup> and later translated into English,<sup>30</sup> German,<sup>28</sup> Polish,<sup>31</sup> and Spanish.<sup>20</sup> Based on the above reviews, all the translated versions had a satisfactory internal validity and consistency. The VQLQ-P, which was developed in this study, also showed suitable internal validity and consistency. The instrument's internal consistency was determined using Cronbach's alpha coefficient. The results suggested that the questionnaire's reliability was adequate.

Individuals between the ages of 20 to 40 made up more than half of the total. The sample was made up of 60% men and 40% women. The findings showed that patients' quality of life is impacted by allergies in the four dimensions: 1) fear and anxiety, 2) social activity, 3) outdoor activity, and 4) leisure. In the present study, the most significant impact on the quality of life was due to fear, anxiety, and disturbance in outdoor activities.

No significant correlation was found between HRQoL and age of the respondents in this study. Also, the unfavorable HRQoL was higher in women. Conflicting results for gender have been seen in different studies. Some studies<sup>32</sup> have reported a greater impact on HRQoL in women, while others have reported conflicting results.<sup>20</sup> The findings of this study are consistent with the findings of a previous study.<sup>31</sup>

In another study, VQLQ were distributed among 87 patients suffering from bee anaphylaxis in the Netherlands. In this case, a clear correlation between the severity of anaphylactic reactions and the level of the patients' anxiety was observed.<sup>33</sup>

Anaphylaxis is graded from 1 (mild) to 4 (severe), with 1 indicating dermatological symptoms, a mild fever reaction, or both, and 4 indicating cardiac or respiratory arrest. Severe anaphylaxis has the potential to become life-threatening and reach peak severity within 10 minutes. A significant relationship between reaction severity and HRQoL impairment was found especially among those with severe anaphylaxis.<sup>18</sup>

In addition, based on the results of a study conducted in Germany in 2009 and using the cross-cultural translation of the HRQoL questionnaire for 84 participants, these patients impose a significant psychological burden on the health of society. They become less productive in the community and cause economic burden to the country and society by missing work, especially in occupations that involve working outdoors and in nature.

Since VQLQ-P highlights the negative impacts of this disease on quality of life, it could lead to planning to improve the health of afflicted individuals in order to take required preventative actions and, eventually, lower the economic burden and expenses of this condition. VIT has improved HRQoL in wasp venom-allergic patients.<sup>32</sup> Consequently, it is probable that VQLQ-P can also be utilized to quantify VIT results in Persian-speaking patients.

In another study, disempowering beliefs related to the fear of a systemic reaction were observed even in a venom-allergic patient who had previously received VIT.<sup>19</sup> In two recent studies,<sup>32,34</sup> HRQoL, measured by VQLQ was significantly improved in patients with HVA concomitantly receiving VIT. Consequently, VQLQ may be relevant and used to evaluate the cost-effectiveness of VIT.

The HRQoL questionnaire was translated and validated in Portugal in 2017 and distributed among 73 patients with HVA, and the obvious influence of the results on the HRQoL and the resulting social and psychological burden was noted. This will allocate greater priority to desensitization of these individuals.<sup>35</sup>

In a study analyzing the economic burden associated with VIT<sup>31</sup> the life-saving aspect of VIT was practically limited by the lack of studies evaluating HRQoL. As expected, it was associated with the highest rate of quality-adjusted life-year (QALY).<sup>36</sup> Yet, this approach of solely relying on survival data for cost-effectiveness evaluation has faced criticism for not adequately reflecting its specific effects on HRQoL.<sup>37</sup>

Therefore, VQLQ-P can play a role in patient-centered approach to decision-making when considering VIT. Determining QALY in this population and evaluating the specific HRQoL in patients allergic to Hymenoptera venom can be helpful from the point of view of financial support to this treatment by healthcare systems.

Our study has some restrictions, including a small sample size. Moreover, the cross-sectional design of this study prevented determining if this instrument can evaluate a change in the QoL in response to an intervention, such as VIT. Nevertheless, in the initial questionnaire, by measuring VIT, clinical improvement in HRQoL was specified and determined.<sup>13</sup> Moreover, the lack of cooperation of several patients in completing the questionnaire and their omission from the study, failure to respond to the questionnaire in person due to the COVID-19 pandemic, and receiving responses over the phone, were among other limitations of this study.

Another potential limitation of our study is the possibility that people living in urban areas may have less concern for the issues examined, leading to a weaker correlation in the results from urban populations compared to the stronger correlations observed in rural populations. However, due to the lack of data on participants' residential areas in our study, we were unable to assess this hypothesis. In addition, individuals with HVA avoid going on vacations to locations where there is a possibility of encountering wasps or bees and prefer to stay at home.

The relationship between the environment and stress and anxiety is emphasized in VQLQ; nonetheless, comparative investigations with various environment settings and populations may be required for precise categorization, as previously noted.

For this questionnaire to be used in the future, longitudinal validation with larger sample size and a multicentered approach is required.

The VQLQ-P can be used in future research and clinical assessment of HRQoL in patients with HVA in Iran and other Persian-speaking regions. The results also indicate that bee allergy has a considerable impact on psychological conditions and has a significant effect on a person's occupational, professional, social, and executive functioning. Furthermore, severe anxiety and fear brought on by frequent anaphylactic reactions disrupt the sense of security and comfort in these patients, resulting in an unsatisfactory HRQoL.

The necessary and appropriate use of VQLQ-P in the first evaluation of a patient with HVA has the advantage of potentially providing the necessary information to the allergist to effectively increase the patient's confidence and aid their decision of whether to initiate VIT.

### STATEMENT OF ETHICS

The authors declare that informed consent was obtained from all patients, and the study protocol was approved by the research ethics committees of the participating centers (Ethics Committee Approval Code: IR.IUMS.REC.1400.112; dated: 20 April 2021).

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This research did not receive funding.

### CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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