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*Clinical Research*

# An International Delphi Consensus on Diagnostic Criteria for Buerger's Disease

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**Background:** Buerger's disease (BD) remains a debilitating condition. Despite multiple published diagnostic criteria for BD, none is universally accepted as a gold standard.

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**Methods:** We conducted a 2-round modified Delphi consensus study to establish a consensus on the diagnostic. The questionnaire included statements from several commonly used diagnostic criteria for BD. Qualitative and quantitative analysis methods were performed. An agreement level of 70% was applied.

**Results:** Twenty nine experts from 18 countries participated in this study. Overall, 75 statements were circulated in Round 1. Of these, 28% of statements were accepted. Following comments, 21 statements were recirculated in Round 2 and 90% were accepted. Although more than 90% of the experts did not agree that the diagnosis of BD can be based only on clinical manifestation, none of the nonclinical manifestations of BD were agreed as a part of the diagnostic criteria. There was an agreement that a history of tobacco consumption in any form, not necessarily confined to the current use, should be a part of the diagnostic criteria of BD. The history of thrombophlebitis migrans, even if not present at presentation, was accepted as a clue for BD diagnosis. It was also agreed that discoloration of the toes or fingers could be included in the diagnostic criteria of BD. Experts agreed that histology results could differentiate BD from atherosclerosis obliterans and other types of vasculitis. The presence of corkscrew collaterals on imaging and burning pain reached the agreement at the first round but not at the second. There was no consensus regarding age cut-off, the requirement of normal lipid profile, and normal blood glucose for BD diagnosis.

**Conclusions:** The present study demonstrated discrepancies in the various published diagnostic criteria for BD and their selective utilization in routine clinical practice worldwide. We propose that all published diagnostic criteria for BD be re-evaluated for harmonization and universal use.

## INTRODUCTION

Buerger's disease (BD) remains a condition that ultimately results in a minor or major amputation with a significant negative impact on quality of life and socioeconomic ramifications.[1] The geographical distribution of BD is unclear but appears to be more prevalent in the Middle East, South-East Asia, and Eastern Europe.[2] This apparent distinct geographical distribution may be attributed to genetic predisposition and the diagnostic criteria used. In the Middle East and South Asia, Shionoya's criteria are the most commonly used diagnostic criteria.[3] In contrast, Olin's criteria are the most used in Europe.[3]

At present, there are no universally agreed on diagnostic criteria for BD. To our knowledge, there is no study that was collaborated by so many international experts who discussed and agreed on the diagnostic criteria for BD. The main objective of this study is to perform a Delphi consensus survey to discuss and agree on the key features which are sufficient to contribute to the definition of the diagnostic criteria for BD. The Delphi method is a process for gaining consensus through controlled feedback from a panel, consisting of a group of experts or individuals knowledgeable on the subject.[4] For this study, we used the Delphi method by inviting experts in angiology/vascular surgery from different international regions.

## METHODS

A modified Delphi consensus survey questionnaire was conducted using 2 rounds of 75 questions and an online consensus meeting. This Delphi consensus survey is a valid method to gather consensus from experts and includes the establishment of effective communications and solicitation of opinions from experts in BD to identify the optimal diagnostic criteria for BD.[4]

### Selection of Participants

Following a nonprobabilistic sampling approach, a total of 40 international experts with different professional backgrounds from 23 countries were invited to participate in the study to gather a broad range of opinions to reach a consensus. Participants were included based on their reputation and involvement in research and/or clinical practice related to BD (Table I). Specifically, invitees who had published research articles or audits on the topic or were clinical practitioners who had recognized expertise in managing BD were included. In addition, participants had to have published peer-reviewed research papers within the last 5 years in this area or had at least 10 years of experience in providing care for patients with BD. To ensure that the participation of experts in this Delphi consensus survey reflected the broad range of BD

**Table I.** Characteristics of the participants

| Characteristics | *n* | % |
|---|---|---|
| Gender | | |
| Female | 1 | 3.5% |
| Male | 28 | 97% |
| Career stage | | |
| Early-stage career (< 10 years) | 2 | 7% |
| Late-stage career (> 10 years) | 26 | 93% |
| Country | | |
| Austria | 1 | 3.5% |
| Bangladesh | 1 | 3.5% |
| Croatia | 1 | 3.5% |
| Egypt | 1 | 3.5% |
| Germany | 2 | 7% |
| Hungary | 1 (core group) | (core group) |
| India | 7 | 25% |
| Iran | 2 + 1 (core group) | 7% (core group) |
| Ireland | 1 (core group) | (core group) |
| Italy | 1 + 1 (core group) | 3.5% + (core group) |
| Japan | 1 | 3.5% |
| Nepal | 1 | 3.5% |
| Oman | 1 | 3.5% |
| Poland | 2 | 7% |
| Romania | 1 | 3.5% |
| Saudi Arabia | 1 | 3.5% |
| Singapore | 1 | 3.5% |
| Slovenia | 2 (core group) | (core group) |
| Syria | 1 | 3.5% |
| Thailand | 1 | 3.5% |
| Turkey | 3 | 10% |
| Native English speaker | | |
| Yes | 0 | 0 |
| No | 29 | 100% |
| Number of peer-reviewed papers on BD | Mean: 3 papers<br>Maximum: 18<br>Minimum: 0 | |
| Number of patients with BD treateds | Mean: 300 patients<br>Maximum: >1,000<br>Minimum: 3 | |
| Area of expertise | | |
| Angiology | 7 | 24% |
| Vascular Surgery | 19 | 66% |
| Cardiovascular Surgery | 3 | 10% |

domains, the backgrounds of participants included clinicians, academic researchers, and educators with expertise in different aspects of BD management was considered most important. The core working group was from Hungary, Iran, Ireland, Italy, and Slovenia (Z.P., B.F., A.L., M.C., M.K., and P.P.). Selected participants were sent invitations via e-mails. Interested individuals were provided with additional information and invited to participate in a web-meeting to introduce and discuss the methods. Two sessions were conducted to suit participants from multiple time zones. Time was allowed to consider participation before receiving the Delphi consensus survey.

## Development and Administration of the Questionnaires

A systematic review was conducted before the Delphi consensus survey to identify the current diagnostic criteria for BD in the literature, from the initial literature by Leo Buerger till January 2021. From the systematic review, other commonly used diagnostic criteria for BD, including Shionoya's

**Table II.** The results of the first and second rounds of the Delphi consensus survey

| | | First round | | | Second round | | |
|---|---|---|---|---|---|---|---|
| No | Question | Agree (%) | Disagree (%) | No idea (%) | Agree (%) | Disagree (%) | No idea (%) |
| 1 | The TAO diagnosis should be based on clinical manifestations only. | 25 | 75 | 0 | **15** | **85** | **0** |
| 6 | The history of smoking in current nonsmoker patients is acceptable for TAO diagnosis. | 90 | 10 | 0 | **100** | **0** | **0** |
| 7 | The history of consumption of any type of tobacco is necessary for TAO diagnosis. | 90 | 10 | 0 | **90** | **10** | **0** |
| 9 | The history of facing with any kind of smoke (like fire smoke) is acceptable for TAO diagnosis in nonsmokers. | 21 | 70 | 9 | **16** | **70** | **14** |
| 16 | TAO diagnosis should be excluded if the patient does not have upper limb involvement or thrombophlebitis migrans. | 14 | 86 | 0 | **10** | **90** | **0** |
| 17 | The history of thrombophlebitis migrans as the temporary tender and reddish lesions on the lower or upper limbs is acceptable for TAO diagnosis. | 75 | 21 | 4 | **92** | **8** | **0** |
| 24 | Poor oral hygiene is necessary for TAO diagnosis. | 25 | 71 | 4 | **19** | **81** | **0** |
| 25 | The quality of pain (burning pain) should be considered for TAO diagnosis. | 72 | 25 | 3 | **68** | **32** | **0** |
| 26 | Discoloration of the toes or fingers should be considered for TAO diagnosis. | 79 | 21 | 0 | **72** | **20** | **8** |
| 29 | Borderline fast blood sugar (100−125 mg/dl) excludes TAO diagnosis. | 19 | 78 | 3 | **4** | **96** | **0** |
| 31 | The value of total cholesterol is enough for TAO diagnosis. | 11 | 82 | 7 | **0** | **100** | **0** |
| 33 | Low HDL (< 35 mg/dl) excludes TAO diagnosis. | 15 | 78 | 7 | **0** | **100** | **0** |
| 34 | Blood sugar and lipids are enough for TAO diagnosis. | 7 | 90 | 3 | **4** | **96** | **0** |
| 46 | Negative erythrocyte sedimentation rate is necessary for TAO diagnosis. | 25 | 75 | 0 | **0** | **100** | **0** |
| 47 | Negative C-reactive protein is necessary for TAO diagnosis. | 18 | 79 | 3 | **0** | **96** | **4** |
| 51 | Duplex sonography is enough for confirming TAO diagnosis. | 25 | 71 | 4 | **8** | **92** | **0** |
| 52 | From imaging, duplex sonography is the first choice for evaluating TAO diagnosis. | 71 | 25 | 4 | **72** | **28** | **0** |
| 58 | From imaging, CE-MRA is the first choice for evaluating TAO diagnosis. | 7 | 86 | 7 | **10** | **90** | **0** |
| 65 | Occlusion of suprapopliteal arteries excludes TAO diagnosis. | 18 | 82 | 0 | **10** | **90** | **0** |
| 71 | Pathology study can confirm TAO diagnosis. | 93 | 7 | 0 | **90** | **10** | **0** |
| 72 | Pathology study can differentiate TAO from other types of vasculitis. | 86 | 11 | 3 | **90** | **7** | **3** |
| 73 | Pathology study can differentiate TAO from ASO. | 81 | 4 | 15 | **100** | **0** | **0** |

The results of the second round have been bolded.

criteria,[5] Olin's criteria,[6] Mill's criteria,[7] and Papa's scoring system,[8] were also included in the survey. Of these diagnostic criteria, a list of 75 statements and one open-ended question were generated and included in the first survey. Questions in English were categorized into 4 sections: clinical signs and symptoms (26 statements), laboratory data (23 statements), radiological data (21 statements), and histological data (5 statements). Participants were given 3 weeks to respond to each round. To improve the response rate, weekly reminders were sent to those who had not yet responded.

### Delphi Rounds

The first and second Delphi rounds were circulated on May 20, 2021 and September 20, 2021. Participants were asked to rate the statements with a ternary response ('agree,' 'disagree,' or 'no idea') and add free-text comments, if necessary. An agreement level of 70% was used as a threshold for accepting the statements.[9] Statements not meeting this criterion were automatically excluded. The free-text comments in Round 1 were collated and mapped with the existing statements or refined as new statements to be circulated in Round 2. The final set of statements was forwarded to participants in advance of the online consensus meeting.

### Consensus Meeting

Participants were invited to the online expert panel at the end of the second Delphi round on October 22, 2021 to refine the final statements and minimize duplication or repetition. Additional clinicians with expertise in BD were invited to participate in the meeting as external experts and act as a sounding board.

## RESULTS

### Characteristics of the Participants

Forty international experts with different professional backgrounds from 23 countries were invited to participate in the study. Thirty experts from 18 countries participated and contributed to Round 1 (response rate = 75%). Their area of expertise was angiology (24%), vascular surgery (66%), and cardiovascular surgery (10%). None of the participants were native English speakers. A total of 29 experts from 18 countries participated in Round 2 (response rate = 96.6%). Table I summarizes the characteristics of the participants.

### Results of Rounds 1 and 2

The first and second Delphi rounds results are summarized in Appendix 1 and Table II. Notably, no significant difference was found between the responses of experts from European countries in comparison to those from non-European countries ($P > 0.1$). Furthermore, no significant difference was found between the responses of surgeons and angiologists ($P > 0.1$). More than 70% of the experts disagreed that the diagnosis of BD is made based on clinical manifestation only.

### Consensus about Demographic and Smoking Variables

Notably, the BD onset age was not considered an inclusion or an exclusion criterion. Only 50% agreed to include the low socioeconomic status of the patient as an inclusion criterion. Notably, about 90% agreed that a history of any tobacco consumption was necessary for BD diagnosis even in the current nonsmokers. However, there was less than 70% agreement on current/passive smoking or cannabis use as inclusion criteria.

### Consensus about Clinical Features

There was no agreement on ischemic involvement of the lower limbs, absence of distal pulses of the lower limbs, ankle-brachial index less than 0.9, and vasomotor symptoms for BD diagnosis. One of the experts recommended revising the item of ''involvement of the lower limb'' into ''involvement of both upper and lower limbs.''

More than 80% disagreed with excluding BD if the patient does not have upper limb involvement or thrombophlebitis migrans. Although this statement was one of the items of Shionoya's criteria, one of the experts recommended that it was necessary to describe upper limb involvement.

More than 70% agreed that a history of thrombophlebitis migrans as the temporary tender and reddish lesions on the lower or upper limbs is acceptable for BD diagnosis. However, less than 70% agreed to consider hyperpigmentation on the line of superficial veins of extremities as thrombophlebitis migrans.

More than 70% agreed that discoloration of the toes and fingers, but not rubor, can be considered for BD diagnosis. More than 70% agreed to consider the quality of pain in BD (burning pain) as the inclusion criteria in the first round. However, this agreement was reduced to 68% in the second round. Interestingly, more than 90% disagreed that the absence of popliteal pulse excluded BD diagnosis.

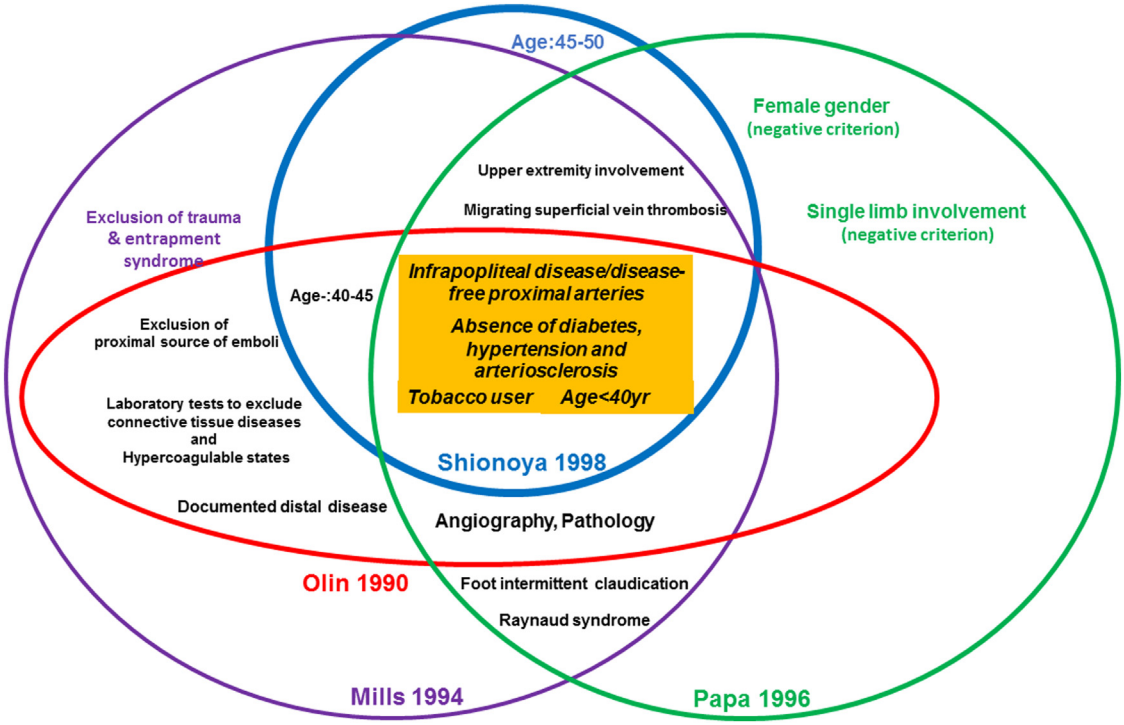


**Fig. 1.** The 4 main diagnostic criteria and scoring system for TAO with their overlaps highlighted in a yellow box.

The agreement on considering hypertension as a criterion for BD was less than 40.

## Consensus about Clinical Investigations

Although 85% disagreed to diagnose BD based on clinical manifestation only in the second round, the agreement for using paraclinical investigation including laboratory tests, imaging, and pathology for BD diagnosis was less than 60%.

## Laboratory

From the laboratory data perspective, more than 70% disagreed that the borderline fasting blood glucose level (100−125 mg/dl) or dyslipidemia (HDL cholesterol < 35 mg/dl) could be used to exclude BD diagnosis. Also, more than 70% disagreed with excluding BD diagnosis if the patient had a positive erythrocyte sedimentation rate or positive C-reactive protein test. For the rest of the laboratory tests, including diabetes mellitus (DM), hyperlipidemia, hypercoagulable state, infections (HBV, HCV, HIV, and syphilis), and autoantibodies (ANA, ANCA, ACA, and Anti-Beta2Glycoprotein), the agreement or disagreement to consider them as exclusion criteria were less than 70%. One of the experts recommended evaluating anticentromere and anti-Scl-70 antibodies for excluding scleroderma.

## Imaging

For imaging, only duplex sonography got the consensus as to the first choice for evaluating BD diagnosis. Although, more than 70% agreed that duplex sonography is not enough for BD diagnosis. CT-angiography, conventional angiography, and MR-angiograph were not considered necessary as the first choice investigations for the diagnosis of BD. Notably, the agreement for excluding BD in the presence of atherosclerotic plaque in any imaging was only 48%. However, about 82% of the experts disagreed that occlusion of suprapopliteal arteries excludes BD diagnosis. Generalized vasospasm, Martorell's sign, or skip lesions were not agreed to be necessary for BD diagnosis. In the first round of Delphi, about 74% agreed that corkscrew collaterals were necessary for BD diagnosis. However, the agreement was reduced to 69% in the second round.

## Histology

About 90% of the experts agreed that histology data could confirm BD diagnosis and differentiate it from vasculitis or atherosclerosis. Finally, less than 70%

**Table III.** The consensus of the experts on the overlaps of 4 well-known criteria including Shionoya, Olin, Mill's criteria, and Papa score

| Statement | Overlaps | Consensus |
|---|---|---|
| Tobacco Consumption | S, O, M, P | Agree |
| Cut off for age of disease onset | S, O, M, P | No consensus |
| Limited of vascular involvement to infrapopliteal arteries | S, O, M, P | Disagree |
| Normal proximal arteries (absence of atherosclerotic plaque) | S, O, M, P | No consensus |
| Absence of diabetes | S, O, M, P | No consensus |
| Absence of hypertension | S, O, M, P | No consensus |
| Absence of hyperlipidemia | S, P | No consensus |
| Involvement of upper limbs or thrombophlebitis migrans | S, M, P | No consensus |
| Evaluating hypercoagulable states | O, M | No consensus |
| Evaluating autoantibodies | O, M | No consensus |
| Documented distal disease by imaging | O, M | No consensus |

S, Shionoya; O, Olin; M, Mills; P, Papa.

agreed that histology studies of amputees or superficial thrombophlebitis are needed to diagnose BD.

## DISCUSSION

Several diagnostic criteria have been used for the diagnosis of BD worldwide. Some of these are newer criteria, but Olin's criteria have been accepted for BD diagnosis for more than 2 decades. Despite being used globally, none of these diagnostic criteria have been validated. This study aimed at specialists in the field of vascular medicine or vascular surgery to discuss and agree on the key features which are sufficient to contribute to the definition of the diagnostic criteria for BD diagnosis in their daily practice.

Figure 1 shows the overlaps of the 4 most well-known BD diagnostic criteria, including Shionoya's criteria,[5] Olin's criteria,[6] Mill's criteria,[7] and Papa's scoring system.[8] Overall, the age of disease onset before 40 years, involvement of crural arteries with normal proximal arteries, a history of tobacco consumption, especially tobacco smoking, and the absence of diabetes and evidence of atherosclerosis are the common features in all these 4 criteria.

Notably, as per the present study, the experts agreed on the history of smoking and disagreed about the limitation of vascular involvement of lower limbs to infrapopliteal arteries. There was no consensus regarding the rest of the other items, including upper limb involvement, thrombophlebitis migrans, exclusion of DM, hypertension, hyperlipidemia, hypercoagulable states, and autoimmunity. Table III shows the opinion of the experts about these overlaps.

The absence of the consensus might support different experience of the experts on BD diagnosis. For instance, concerning the age of disease onset, 2 opposite studies were focusing on the age of disease onset of BD. One study is in South Korea, consisting of 24,392 patients with newly diagnosed BD based on the exclusion of atherosclerosis and a typical angiography. In that study, 80% of the patients were aged more than 50 years.[9] In contrast, as per a study on 377 BD patients in Poland, the age of onset remains consistently less than 50 years.[10]

In this study, although most of the experts agreed that BD should not be diagnosed based on clinical manifestations, there was no consensus about the necessity of clinical investigation for BD diagnosis.

Similarly, there was no consensus regarding laboratory evaluation for excluding atherosclerosis risk factors such as DM, hyperlipidemia, and hypertension, excluding hypercoagulable states and evaluating other autoantibodies. Notably, there are several reports of hyperlipidemia and DM in patients with BD.[11–13] As per these reports, the diagnosis had been made based on ischemic involvement of both lower and upper limbs and typical angiography.[11–13] An abrupt occlusion of infrapopliteal arteries, absence of calcification, and cork-screw collaterals were the main objects for considering an angiographic appearance in a patient with BD.[13]

Concerning imaging, although there was a consensus that duplex sonography was the first choice for evaluating BD, none of the imaging, including duplex sonography, CT-angiography, angiography, or magnetic resonance angiography, got the consensus to be necessary for confirming BD diagnosis. Angiographic demonstration of vaso-constriction, absence of atherosclerotic plaque, corkscrew collaterals, and skip lesions did not reach the necessary consensus for diagnosis of BD. Notably, about 21% could not decide about Martorel's sign. Maybe further studies on evaluating Martorel's sign in BD patients' angiograms compared

to other types of vasculitis or peripheral arterial disease can lead to a consensus to consider if this sign would or would not confirm BD.

Although a part of the most well-known diagnostic criteria for BD was exclusion criteria, there was no consensus for exclusive items such as DM. On the other hand, as per the 4 well-known diagnostic criteria, BD and DM were mutually exclusive and could not occur simultaneously. In contrast, the present study results suggest that they might not be mutually exclusive.

Moreover, for several statements, a considerable number of experts had no agreed consensus. For instance, about the use of cannabis, 37% had no idea if it could cause the clinical and paraclinical features of BD. Also, a considerable number of experts had no agreement about laboratory tests. Therefore, it seems that more data from different regions are necessary for reaching a consensus about the possibility of other triggers for the development of BD such as infection or use of cannabis or about other clinical laboratory tests as exclusion criteria for BD.

In summary, it is time to re-evaluate the older diagnostic criteria for BD based on the overall finding of our study. Furthermore, there is an urgent need to determine if BD and atherosclerosis/autoimmunity/hypercoagulable states are mutually exclusive.

This study has several limitations. First, there were a finite number of global experts in BD given the rarity of BD. Second, although participation in this Delphi survey was voluntary, a high attrition rate was expected.[14] This might result in over-representation or under-representation of specific perspectives. The overall results of this Delphi survey represent the opinion of those who have agreed to participate, which is inherently associated with an unintentional bias. However, the analysis of the results of this Delphi survey and the consultation with external experts arrived at a similar and consistent conclusion.

The main strength of this study is that this is the first Delphi survey that included experts from various countries to agree on the diagnostic criteria for BD. This will serve as a template and catalyst for the first expert consensus guidelines. Also, the region and specialty of the participants did not influence the overall result of the study.

## CONCLUSION

The present study showed a discrepancy in the various published diagnostic criteria for BD and their utilization in routine clinical practice. All published diagnostic criteria for BD require to be re-evaluated for harmonization and universal use.

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## SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.avsg.2022.03.028.

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