Title: Population-Based Utility of van Herick Grading for Angle Closure Detection

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Running head: Utility of van Herick grading for angle closure detection

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Human subjects: Human subjects were included in this study. The ZAP trial was approved by the Ethical Review Board of Sun Yat-Sen University, the Ethical Committee of Zhongshan Ophthalmic Center, and the Moorfields Eye Hospital and Johns Hopkins University institutional review boards. This trial was done in accordance

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with the tenets of the Declaration of Helsinki. All study participants provided informed consent at the time of enrollment.

No animal subjects were used in this study.

Author contributions:

Conception and design: Halawa, Zebardast, Foster, He, Aung, Friedman Data collection: Halawa, Zebardast, Kolli, Foster, He, Aung, Friedman Analysis and interpretation: Halawa, Zebardast, Kolli

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This article contains additional online-only material. The following should appear online only: Supplemental Table 1, Supplemental Figure 1.

Unstructured abstract: We report the sensitivity and specificity of van Herick (VH) grading in detecting gonioscopically-defined primary angle closure suspects (PACS) among subjects screened for participation in a population-based trial in southern China. A cutoff of VH≤25% was found to have sensitivity and specificity rates of 98.2% and 25.9%, respectively. Rates were adjusted for missing gonioscopy data, resulting in a sensitivity and specificity of 92.5% and 61.5%, respectively.

Primary angle closure glaucoma accounts for half of glaucoma-related blindness worldwide with a disproportionate burden of disease found in Asian populations.[1] The clinical reference standard for diagnosis of angle closure is gonioscopy, but van Herick (VH) grading of limbal anterior chamber depth (LACD) has been used as a screening tool, with varying sensitivities and specificities on classifying gonioscopically occludable angles reported in Chinese and other East Asian populations.[2] A cutoff of VH grade ≤1 (modified grade ≤15%) has been found to have sensitivities ranging from 19% to 84% and specificities from 86% to 100%, whereas a higher cutoff VH grade ≤2 (modified grade ≤25%) has had sensitivities ranging from 54% to 99% and specificities from 65% to 96%.[2] However, the efficacy of using VH test as a screening tool in community-based screening programs to identify gonioscopically occludable angle has not yet been investigated. The purpose of this study was to determine the sensitivity and specificity of modified van Herick grading of LACD in detecting gonioscopically-defined primary angle closure suspects (PACS) among subjects screened for participation in the Zhongshan Angle Closure Prevention (ZAP) Trial in southern China.

Potential study participants underwent a screening evaluation for the ZAP Trial registered as 'ISRCTN45213099-Zhongshan Angle-closure Prevention Study' (http://www.controlled-trials.com/ISRCTN45213099).[3] Recruitment began in June 2008 and ended in October 2010. Limbal anterior chamber depth (LACD) was evaluated by a VH grading system using a slit lamp (BQ-900, Haag-Streit, Switzerland)**.** The traditional VH grading system was modified by expressing the depth of the temporal anterior chamber at the corneoscleral junction as a percent of the adjacent corneal thickness using a set of standard reference photographs (modified grades of 5% and 15%

corresponded to a traditional grade of 1; 25% corresponded to a traditional grade of 2; 40% and 75% corresponded toa. Traditional grade of 3; and 100% corresponded to a traditional grade of 4). A modified VH grading system was chosen to standardize grading across examiners. Eyes with a VH grade ≤25% underwent gonioscopy to evaluate for presence of PACS defined as having a Shaffer grade <2 in ≥180 degrees on gonioscopy. Those with a VH grade >25% underwent gonioscopy only if narrow angles were suspected upon further evaluation with the Scanning Peripheral Anterior Chamber depth analyzer (SPAC; numerical grade ≤6 or categorical grade P or S).[4] Gonioscopy was performed by 1 glaucoma-trained ophthalmologist who had high reliability when compared with glaucoma specialists with more than 10 years of experience conducting angle closure research (weighted kappa>0.80).[3]

Unadjusted sensitivity and specificity in detecting PACS (defined as Shaffer grade <2 in ≥180 degrees on gonioscopy) were calculated for both VH grade ≤15% (equivalent to traditional VH grade≤1) and VH grade ≤25% (equivalent to traditional VH grade ≤2). False-negative rates from existing data were extrapolated to subjects with missing gonioscopy data in order to calculate adjusted sensitivity and specificity rates for the VH≤15% and ≤25% cutoffs. Only measurements of the right eye in all participants were used in these calculations. Positive predictive values. (PPVs) and negative predictive values (NPVs) were calculated using the above VH cutoffs. PPVs and NPVs were also estimated for a range of PACS prevalence based on prior Chinese population-based studies.[5,6] Receiver operating characteristic (ROC) curves were generated for these cutoffs, and the areas under the curve were calculated.

After initial screening for exclusion criteria (previous eye surgery, previous glaucoma treatment, cancer, or other life-threatening disease),[3] 3,734 subjects (7,468 eyes) with best-corrected visual acuity ≥ 20/40 were selected for further evaluation of eligibility to participate in the ZAP study. 2673 subjects (69.1%) were female, and mean age was 59.2 (standard deviation, 5.5). All eyes underwent LACD evaluation using modified VH grading. Among 1795 right eyes with a VH grade ≤25%, 667 (37.2%) met criteria for PACS on gonioscopy. Of the 1899 right eyes with a VH grade >25%, 407 underwent gonioscopy in order to rule out iridotrabecular contact suspected on SPAC, of which 12 eyes (2.9%) were graded PACS on gonioscopy. Classification of right eyes by VH grade and number of quadrants with Shaffer <2 on gonioscopy is shown in Table S1 and Figure S1 (available at http://www.aaojournal.org).

Among right eyes with LACD and gonioscopy findings (2202 eyes), a cutoff of VH≤25% had an unadjusted sensitivity of 98.2% and unadjusted specificity of 25.9% in detecting PACS. By assuming the false-negative rate for all subjects with VH>25%, including those without available gonioscopy data, was 2.9%, a cutoff of VH≤25% would have an adjusted sensitivity and specificity of 92.5% and 61.5%, respectively. Subjects with positive VH test results (≤25%) had a PPV of 37.2% for PACS, and those with negative VH test results (VH>25%) had an NPV of 97.1% for PACS. By assuming a prevalence of 1.5 to 11.4% based on prior Chinese population-based studies, we estimate a PPV of 2.0 to 14.6% and an NPV ranging from 99.1 to 99.9% using the VH≤25 cutoff. A cutoff of VH≤15% had unadjusted sensitivities and specificities of 39.6% and 84.1%, respectively, in detecting PACS. Among the 1519 subjects with VH>15% and missing gonioscopy data, 1492 had a VH>25. Therefore, in calculating

adjusted sensitivity for a cutoff of VH≤15%, the same 2.9% was used to calculate adjusted sensitivity and specificity rates, resulting in adjusted rates of 37.8% and 91.7%, respectively. Subjects with positive VH test result (≤15%) had a PPV of 52.6% for PACS, and those with negative VH test result (VH>15%) had an NPV of 75.8% for PACS. On the basis of the prior reported prevalence of PACS, Chinese population-based PPV is estimated to range from 3.7 to 24.3% and NPV from 91.5 to 98.9% using the VH≤15 cutoff[5,6]. Area under the ROC curve reached 0.62 for a VH cutoff of ≤25% and 0.62 for a VH cutoff of ≤15% (Figure 1). Area under the ROC curve adjusted for missing gonioscopy data was 0.77 for VH cutoff of ≤25% and 0.65 for a VH cutoff of ≤15% (Figure S2, available at http://www.aaojournal.org).

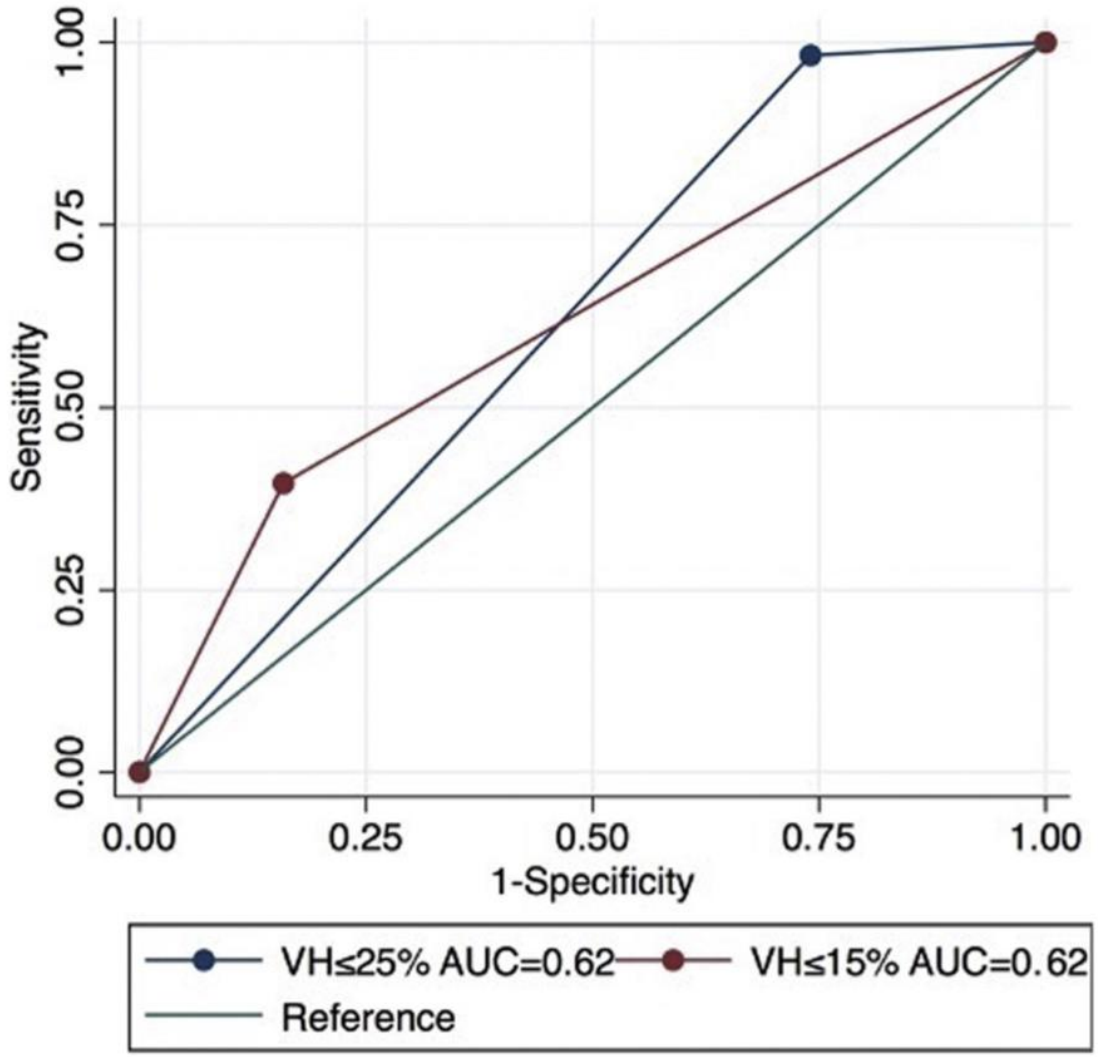
Among subjects screened for participation in the ZAP study in southern China, VH grade was found to be 98.2% sensitive and 25.9% specific in detecting PACS on gonioscopy in the right eye when using a cutoff of ≤25%. A lower cutoff of ≤15% had lower sensitivity but higher specificity and positive predictive value. This is consistent with prior findings showing that sensitivity increased, and specificity decreased, with less stringent LACD cutoff criteria.[2]

Of 1899 right eyes with VH>25%, only 21.4% underwent gonioscopy. Of those, 2.9% were found to have PACS. Because these eyes were selected for gonioscopy based on suspicious SPAC findings, it is likely that the percentage of PACS in this population (i.e., the false-negative rate) is lower than estimated here. We found that adjusted sensitivities and specificities based on a false-negative rate of 2.9% were consistent with previously reported rates.[2] Lower false-negative rates of 1% and 2% among eyes with VH>25 missing gonioscopy data would yield higher sensitivities of

96.2% and 94.2%, respectively, but similar specificities of 61.9% and 61.7%, respectively. The missing gonioscopy data for eyes with VH>25 likely resulted in an underestimated specificity and overestimated sensitivity.

We found that among subjects screened for participation in the ZAP study, the sensitivity and specificity of LACD screening using a VH cutoff of ≤25% for detecting PACS on gonioscopy are consistent with prior reports. The LACD VH grading had 98.2% sensitivity for detecting PACS at a cutoff of ≤25% suggesting this test may be useful for ruling out iridotrabecular contact, especially in a clinic-based setting. However, the low specificity and PPV likely limit its utility as a population-based screening tool, even in populations with a high prevalence, for whom resources may be limited. The high false-positive rate would result in an unsustainable number of individuals requiring further evaluation by gonioscopy. In the ZAP study, LACD screening was intended to be a cost-effective tool to identify as many potential PACS participants as possible. However, a large number of individuals who required follow-up gonioscopy based on LACD findings were not found to have PACS on gonioscopy and were subsequently excluded from the study. Crucially, results from ZAP indicate that early detection of PACS may not have a large public health benefit given the low likelihood of developing acute angle-closure or angle-closure glaucoma.[7]

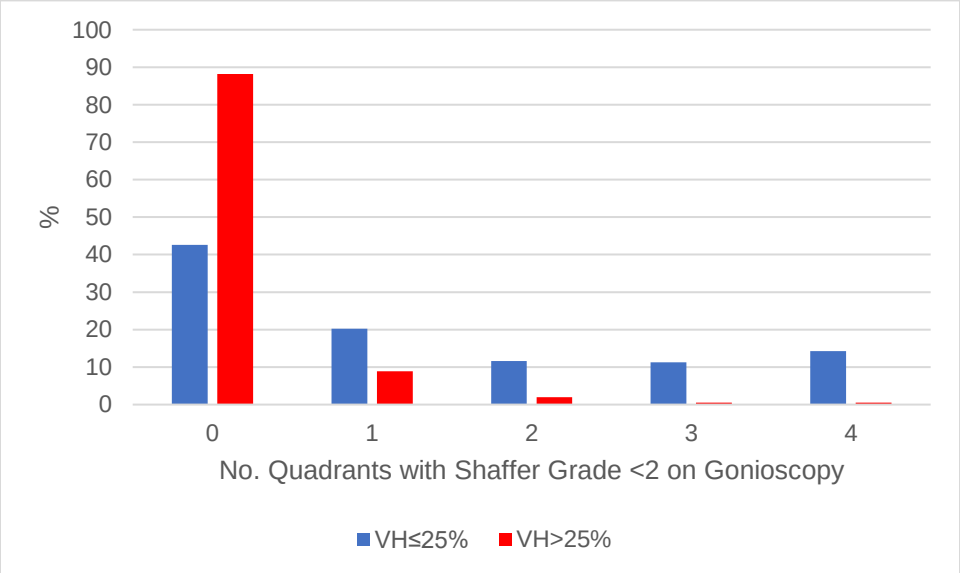
Figure 1: Receiver operating characteristic curve



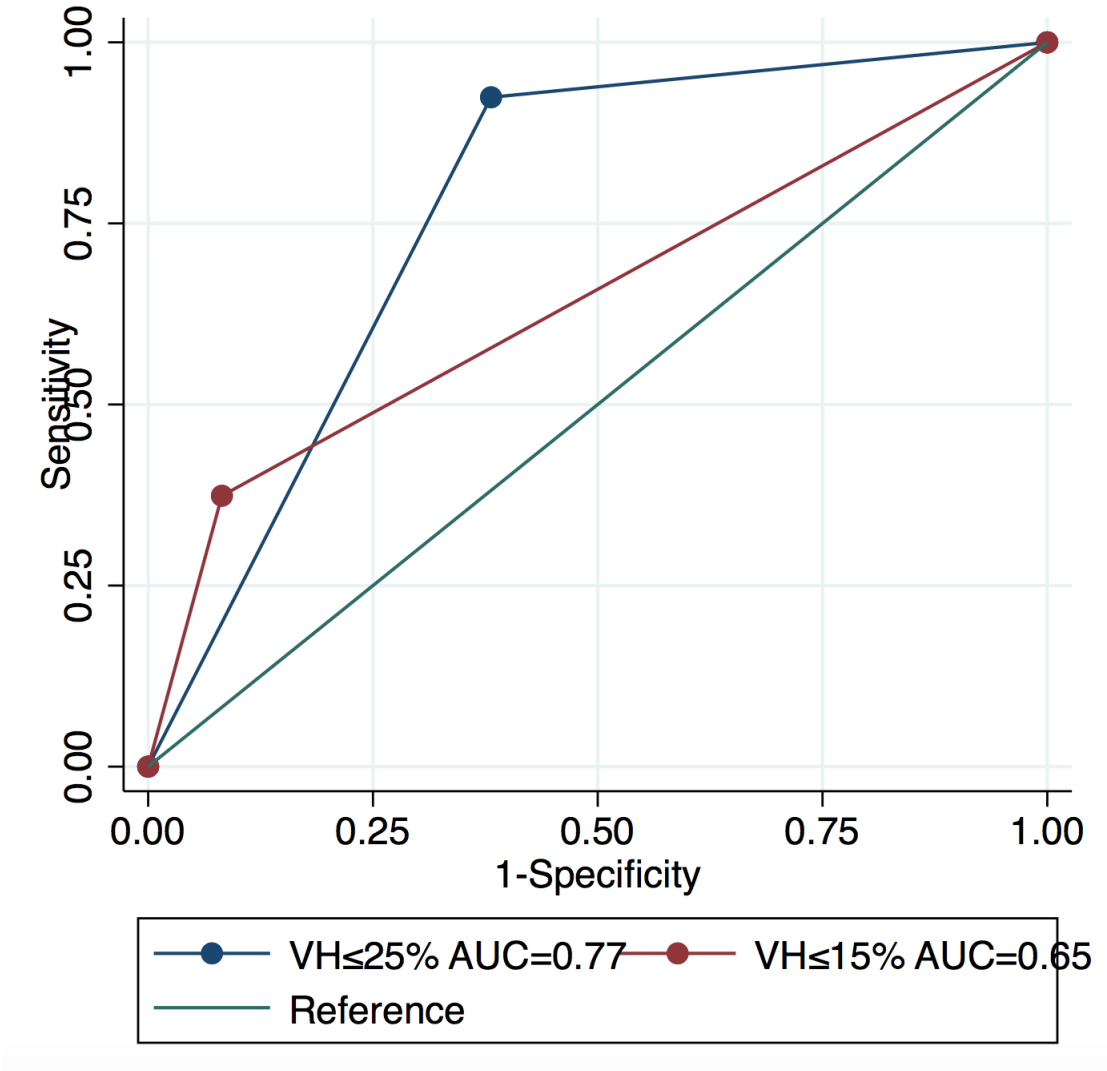
Supplemental Table 1: Right eyes classified by van Herick grade and number of quadrants with Shaffer grade <2 on gonioscopy

VH grade	No. of quadrants with Shaffer <2 on gonioscopy					Gonioscopy unavailable	Total
	0	1	2	3	4		
5% no. (%)	11 (19.6)	12 (21.4)	9 (16.1)	4 (7.1)	17 (30.4)	3 (5.4)	56 (100)
15% no. (%)	126 (26.9)	93 (19.9)	52 (11.1)	61 (13.0)	126 (26.9)	10 (2.1)	468 (100)
25% no. (%)	628 (47.9)	258 (19.7)	148 (11.3)	137 (10.5)	113 (8.6)	27 (2.1)	1,311 (100)
40% no. (%)	246 (26.2)	31 (3.3)	7 (0.7)	2 (0.2)	2 (0.2)	652 (69.4)	940 (100)
75% no. (%)	75 (14.7)	4 (0.8)	0 (0)	0(0)	0 (0)	429 (84.5)	508 (100)
100% no. (%)	38 (8.4)	1 (0.2)	1 (0.2)	0 (0)	0 (0)	411 (91.1)	451 (100)
Total	1,124 (30.1)	399 (10.7)	217 (5.8)	204 (5.5)	258 (6.9)	1,532 (41.0)	3,734 (100)

Supplemental Figure 1: Distribution of number of quadrants with Shaffer<2 stratified by VH grade ≤ 25% and >25% in all right eyes



Supplemental Figure 2: Receiver operating characteristic curve, adjusted for missing gonioscopy data



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