

# Normal reference intervals of prognostic nutritional index in healthy adults: A large multi-center observational study from Western China

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## Research Article

**Keywords:** Reference interval, Prognostic nutritional index, Cohort study

**Posted Date:** January 8th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-135449/v1>

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## Abstract

# Background

It has been widely reported that the prognostic nutritional index (PNI) played a pivotal role in nutritional assessment of surgical patients and tumor prognosis. In order to improve the accuracy of evaluation in western China, we established reference intervals (RIs) of PNI in healthy controls.

## Methods

A retrospective cohort study on healthy ethnic Han adults (18–79 years) was conducted to explore the influences of age, gender, study centers, and instruments on PNI and to establish RIs. The data came from a healthy routine examination center database and laboratory information system (LIS) of four centers in western China, and there were 200 persons selected randomly for verification of RIs.

## Results

5,839 healthy candidates were enrolled. PNI showed a marked gender dependence, and males had significantly higher PNI than females across all ages ( $P < 0.01$ ). We found that PNI is significantly different between age groups ( $P < 0.01$ ), the value of PNI tended to decrease with age increasing. There is also an obvious influence of centers and instruments on PNI ( $P < 0.01$ ).

## Conclusions

We established reference intervals of PNI in healthy Han Chinese population in Western China, and validated successfully. Further established RIs will lead to better standardizations of PNI for clinical applications.

## 1. Introduction

Serum albumin is an objective nutritional indicator reflecting the body's protein reserve level, while total lymphocyte count is also an important indicator of patients' nutrition and immunity. PNI based on serum ALB levels and total peripheral blood lymphocytes was originally used to assess the nutritional and immune status of surgical patients and predict surgical risks [1]. Patients with low PNI scores often have a poor prognosis after gastrointestinal surgery and undergo postoperative complications [2]. However, it was further applied to assess the nutritional status of different types of cancer patients[3]: esophageal carcinoma [4], gastric cancer[5] and lung cancer[6]. In addition, recent studies have shown that PNI is associated with the prognosis of specific lymphoma patients, such as diffuse large B cell lymphoma (DLBCL) [7] and Extranodal natural killer/T cell lymphoma (ENKTL) [8].

However, there are few studies that have attempted to derive the normal reference intervals in healthy adults, and the roles of age, gender and instrument on PNI have not been reported widely. Recently, the test results of blood indicators have also shown obvious regional differences, a previous study has reported that there is an obvious lower platelet count in Chengdu city compared to other regions in China [9]. It is absolutely urgent to establish RIs of PNI to apply it to clinical applications more standard and efficiently for healthy persons in Western China.

## 2. Materials And Methods

### 2.1 Experimental arrangement

The Department of clinical laboratory of Sichuan Cancer Hospital & Institute led to establish reference intervals of prognostic major clinical laboratory items in the Han Chinese population in Western China. A total of four centers were selected to participate in this research study: Chengdu Fifth People's Hospital, the first people's Hospital of Yibin, People's Hospital of Jianyang city, Zigong first people's Hospital. Each hospital was responsible for selecting healthy local candidates, performing tests and collecting samples, the department of clinical laboratory of Sichuan Cancer Hospital & Institute was responsible for project quality assurance.

### 2.2 Inclusion and exclusion of subjects

A retrospective study retrieved the health examination center database and laboratory information system (LIS) of four centers which had been mentioned above, to enroll healthy ethnic Han individuals between 18 and 79 years of age, who took health examination between

January 2017 and June 2017. Healthy candidates were selected based on the inclusion and exclusion criteria as Table 1.

Table 1  
inclusion and exclusion criteria

Inclusion criteria:	
1. Age > 18 years and < 79 years.	
2. Availability of complete required data.	
3. Ethnic Han population.	
4. Matched individuals with age and gender (which mean that gender groups (male group and female group) and every subgroup (18–29, 30–39, 40–49, 50–64 and 65–79 years subgroups) to have an approximately equal number of the individuals.)	
Exclusion criteria:	
1. Presence of any known medical condition (comorbidities).	
2. Pregnancy.	
3. History or continued use of alcohol, tobacco, or oral contraceptives.	
4. Abnormal results of clinical laboratory, such as white blood cell count < 3.0×10 <sup>9</sup> /L or > 12.5×10 <sup>9</sup> /L, Abnormal urinalysis results, etc.	
5. Any surgery within 6 months after enrollment.	
6. Blood donation or transfusion within 4 months of enrollment.	
7 Body mass index (BMI) > 28 kg/m <sup>2</sup> .	

After applying the inclusion and exclusion criteria from LIS, there were 34,931 individuals were recruited, and 5,839 of them were enrolled in the final analysis (Fig. 1). The included subjects were further divided into a training group (consisting of 5639 subjects) and a validation group (consisting of 200 subjects), and each training group comprised the following: 18–29, 30–39, 40–49, 50–64 and 65–79 years (Table 2).

Table 2  
Age-partitioned reference intervals and 95% confidence intervals in training group.

Age (years)	All		Hit-Sys		Sie-Mir		Hit-Mir		CRIs	
	2.5 th	97.5th	2.5th	97.5th	2.5th	97.5th	2.5th	97.5th	2.5th	97.5th
18–29	51.4 (50.6–52.0)	66.3 (65.8–66.8)	50 (49.6–51.1)	65.6 (63.8–66.3)	53.3 (52.7–54.1)	66.3 (64.9–67.7)	53.3 (52.4–55.1)	66.9 (66.0–67.8)	48.7 (NA)	70.6 (NA)
30–39	50.2 (49.8–50.6)	65.3 (64.3–66.2)	49.7 (48.4–50.1)	62.9 (62.3–63.7)	51.1 (50.5–52.6)	66.8 (65.4–67.7)	52.1 (51.3–52.7)	66.5 (65.1–67.6)		
40–65	49.4 (48.9–49.9)	64.0 (63.6–64.3)	48.7 (48.5–49.2)	63.4 (62.8–64.1)	50.5 (50.2–51.4)	64.7 (64.2–65.8)	50.4 (50.2–51.4)	64.7 (64.2–65.8)		
65–79	48.1 (47.5–49.0)	64.0 (63.3–64.2)	47.9 (47.4–48.4)	49.5 (47.8–50.6)	49.5 (47.8–50.6)	64.4 (63.5–65.5)	51.7(51.7,54.0)	NA		

Hit, Hitachi; Sys, Sysmex, Mir, Mindray; Sie, Siemens; CRIs, calculated RIs which were Calculated by data from published literature (PMID: 25769040 and PMID:24058449); NA, not available.

## 2.3 Instruments and measurement parameters

Lymphocyte count was analyzed by BC-6600 (Mindray Medical Electronics Co., Shenzhen, China), and serum albumin value was measured by Sie-2400 biomedical analyzer (Siemens AG, Beijing, Germany) in Jianyang center. the BC-6900 hematology analyzer (Mindray Medical Electronics Co., Shenzhen, China) was used to detect the lymphocyte count and Hit-008008 biomedical analyzer (Hitachi Construction

Machinery, Shanghai, Japan) was applied to detect serum albumin in Chengdu center. While the lymphocyte count was detected by XN-1000 hematology analyzers (Sysmex Corp., Kobe, Japan), and the serum albumin was measured by Hit-7600 biomedical analyzer (Hitachi Construction Machinery, Shanghai, Japan) in Yibin and Zigong centers.

Each candidate fasted for solids and liquids for at least 12 hours. Blood from each participant was drawn into appropriate blood collection tubes by using vacuum tube needles, the K2-EDTA tubes were used for Lymphocyte count, while plain tubes were used for estimating albumin value. Samples collected in plain tubes were separated by centrifugation at 3,000 rpm for 5 minutes. After collection, all specimens were supposed to be tested within 1 hour. The PNI was calculated according to the formula is as follow:  $PNI = \text{serum albumin value (g/L)} + 0.005 * \text{peripheral lymphocyte count (MM3)}$

## 2.4 Identification and validation

For identification of RIs, the value of PNI of all subjects included were calculated based on the formula which was above-mentioned, and we log transform the value of PNI after calculating the value. The Tukey's (1977)  $[Q1 - 1.5 \times IQR, Q3 + 1.5 \times IQR]$  rule was used for insuring the reference values against outliers[10]. We made decisions on partitioning by following Ari Lahti et al' proportion criteria: The subgroup-specific reference intervals should be calculated, if at least one of the four proportions of the subgroup distributions cut off by the reference limits of the combined distribution exceeds 4.1% or lies below 0.9%[11]. In the training group, the RIs (2.5th,97.5th) of PNI by the nonparametric methods, while the validation group was utilized to verify the established RIs. Outsider-rate of validation group  $< 0.10$  is considered successfully and efficient established.

## 2.5 Statistics

The data were analyzed with the statistical programming language R and IBM SPSS Statistics version 20.0 software (IBM Corp., Armonk, NY, USA) [12]. Data were finally reported as a median and interquartile range (IQR), 2.5 percentile and 97.5 percentile, appropriately. And the normal distribution was analyzed by using the Kolmogorov-Smirnov test. Mann-Whitney U test and Kruskal-Wallis test were applied for comparisons of two or more than two groups, while the ggplot2 package was applied to data visualization [13]. We established age-partitioned reference intervals for PNI based on significant correlation and visual identification of the relationship between age and PNI. We calculated 95% of reference intervals by bootstrap in IBM SPSS Statistics version 20. All P values  $< 0.05$  were considered statistically significant.

## 3. Results

### 3.1 Study population summary

As showed in Fig. 1, there were a total of 5839 subjects included our study after excluding the 29,625 subjects according to the criteria outlined. The most common exclusions were incomplete data (n = 11820), unmatched age and gender (n = 6,243), age (n = 3,139), clinical laboratory (n = 5,817), diagnose diseases (n = 1,792) and outliers (n = 238). After exclusions, there were 3006 males and 2633 females in the training group with a mean age of 44 years, while 94 males and 106 females in the validation group with a mean age of 43 years (Fig. 2). We found that PNI was not completely distributed normally (data are not shown) following Kolmogorov-Smirnov test. All P values  $< 0.05$  were considered statistically significant.

### 3.2 Gender-and age-related findings

We analyzed the influence of gender on PNI in the training group, and the significant difference was observed in PNI parameter between the males and females ( $P < 0.05$ , Fig. 3A). While none of the four proportions of the subgroup distributions cut off by the reference limits of the combined distribution exceeded 4.1% (Supplementary table 1). Thus, we concluded that the PNI could be combined to calculate the consensus intervals, regardless of gender.

We analyzed the influence of age on PNI in the training group as well, and we found that the PNI was significantly influenced by age (Fig. 4), while the difference was not observed between 40–49 subgroup and 50–65 subgroup (all  $P < 0.05$ , Fig. 3B). Thus, we combined the two subgroups into a new group: 40–65 subgroup. In partitioning analysis, the largest one of the subgroup proportions outside a common reference limit is 6%, which exceeded 4.1% (Supplementary table 1). It shows that establishing the reference interval of PNI should consider the factor of age.

### 3.3 Center-related and Instrument-related findings

Except for Zigong and Yibin centers, there were significant differences among the other centers in PNI (all  $P < 0.05$ , Fig. 3C). The main reason might be the same Instrument: Sysmex® instrument and Hitachi® instrument were used in Yibin and Zigong center. Moreover, it can be clearly observed that the median value of PNI produced by Sie-Mir® instrument was significantly lower than the value produced with Hit-Mir® instrument, while higher than the value produced with Hit-Sys® instrument (all  $P < 0.05$ , Fig. 3D). However, one of the Hit-Mir subgroup distributions cut off by the reference limits of the combined distribution is 6%, which exceeded 4.1% (Supplementary table 1). Therefore, the factor of instrument should be considered when the reference intervals of PNI was calculated.

### 3.4 Establishing final consensus intervals

Reference intervals (2.5th, 97.5th) and corresponding 95% confidence intervals of PNI was established in the training group (Table 2), with nonparametric methods. In addition, we further included a number of 200 healthy candidates to validate the reference intervals (Table 3). We finally found that proportions of outsiders which are validation values below or beyond established RIs are all  $< 0.01$  (Table 3), which means RIs of PNI is successfully and efficient established.

Table 3  
Validation results of reference intervals of PNI.

Groups	NO.	Range	< DL(n)	>UL(n)	NO. of outsider	OR
18-29y & Hit-Sys	19	51.3–65.8	0	1	1	0.05
18-29y & Sie-Mir	3	59.8–61.7	0	0	0	0
18-29y & Hit-Mir	12	56.8–64.0	0	0	0	0
40-65y & Hit-Sys	57	47.2–66.8	2	3	5	0.088
40-65y & Sie-Mir	15	54.4–65.1	0	1	1	0.067
40-65y & Hit-Mir	19	53.5–61.5	0	0	0	0
65-79y & Hit-Sys	43	46.3–62.1	2	0	2	0.046
65-79y & Sie-Mir	28	49.1–68.2	1	1	2	0.071
65-79y & Hit-Mir	4	54.4–63.3	0	NA	NA	NA

DL, down-limit; UL, upper-limit; M, male; F, female; A, adults; OA, old-adults; OR, outsider –rate.

## 4. Discussion

### 4.1 Main finding

In this research, we defined the values of PNI in four centers with a large population. It was found that the values of PNI decreased with age and varied in different instrument. So, RIs for PNI based on age and instrument were observed in the Han population of western China.

### 4.2 Interpretation

The value of PNI reflects the nutritional status and immune status of the patient, which have profound effects on treatment options and quality of life. A low PNI value indicates that the patient is malnourished and has poor immune function [14]. Serum albumin related to PNI value is the important indicator reflecting the nutritional status of the body, the other related factor: lymphocytes, which participate in the host's immune mechanism to prevent infection by mediating cellular immunity, is an important indicator of the body's immune function. Malnutrition is associated with postoperative complications and can lead to longer wound healing times, may also be related to impaired immune function [15–17]. Therefore, monitoring the body's nutrition and immune status has guiding significance for the efficacy and prognosis judgment.

In this study, we defined the normal RIs of PNI in western China by using a large population-based multi-center study in the training group, and validated the RIs in another small group included new candidates with the same conditions in. Meanwhile, we further studied the effect of study center, instruments, gender and age for RIs of PNI in Western China. We found that the value of PNI changed significantly with gender and age, in addition, there is profound influence of study center and instruments. As all known, with advancing age, there is an increased risk of developing nutritional deficiencies, which could explain the decreasing PNI with increasing age. The bleeding during menstrual cycle might bring the nutritional deficiency, which indicates the lower value of PNI in female. Due to the laboratory conditions, including instrument, reagent, and operators, there might be different among the different center.

## 4.3 Strength and limitation

In the past studies on PNI, there is no unified algorithm for the critical value of PNI. Some studies [18–20] choose 45 ~ 49 as the critical value based on experience, while others [21] may draw the ROC curve to obtain the corresponding maximum Youden index to figure out the cut-off value. It is obvious that our research has developed a reasonable PNI reference value range through a comprehensive study of various factors, which is more clinically meaningful. Even though we validated the RIs in a validation group, a larger validation group need to be set in the future work.

## 4.4 Conclusion

In summary, there is an obvious influence of centers, instruments, age and gender on the value of PNI, while the variations were not clinically significant for the subjects. We establish RIs of PNI in a big-data-based way in our multicenter study for healthy Han Chinese populations in Western China. It will benefit experimental design of the related prognosis analyses a lot and lead to better standardizations of PNI for their clinical applications, which is supposed to be promoted into the routine CBC report.

## Declarations

### Acknowledgements

Funding: This study was supported by the Health and Family Planning Commission of Sichuan Province universal application project (No.20PJ115) and the Science and Technology Bureau of Chengdu technological innovation project (NO. 2019-YF05-01279-SN).

### Author contributions

Li T,Zhu GQ,Luo HC was the guarantor and designed the study; Yang GS,Wang DS,Zu RL,He LB,Zhang GJ,Yu JH,Chen YP participated in the acquisition, analysis, and interpretation of the data, and drafted the initial manuscript; Yin HL,Liao YL,Li S,Deng Y,Zhang KJ revised the article critically for important intellectual content.

### Ethics statement

All experimental protocols were approved by the Ethics Committee of Sichuan Cancer Hospital & Institute, and got the consent of all subjects, the informed consent was obtained from all participants and/or their legal guardians. All experiments were performed in accordance with relevant guidelines and regulations and our research have been performed in accordance with the Declaration of Helsinki.

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## Supplementary Table

Supplementary table 1. Make decisions on partitioning by Ari Lahti et al' proportion criteria

Factors	No.	Combined reference intervals of PNI	
		<49.6 (n, %)	>64.9 (n, %)
<b>Gender</b>			
male	3006	55,2	106, 2
female	2633	79, 3	36, 1
<b>Age bins (years)</b>			
18-29	1211	11, 1	<b>67, 6</b>
30-39	1041	14, 1	31, 3
40-65	2709	71, 3	40, 1
66-79	678	<b>38, 6</b>	4, 1
<b>Instruments</b>			
Hit-Sys	3031	108, 4	34, 1
Sie-Mir	1427	15, 1	41, 3
Hit-Mir	1181	10, 1	<b>67, 6</b>

## Figures

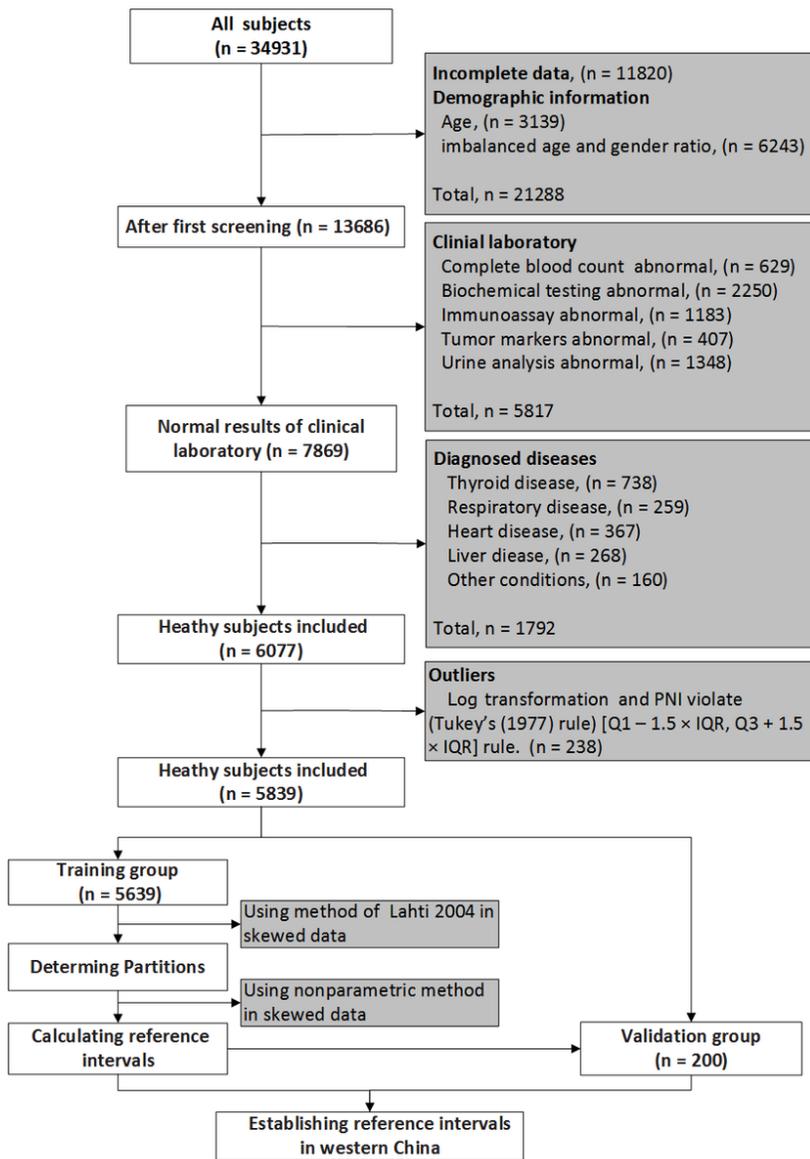
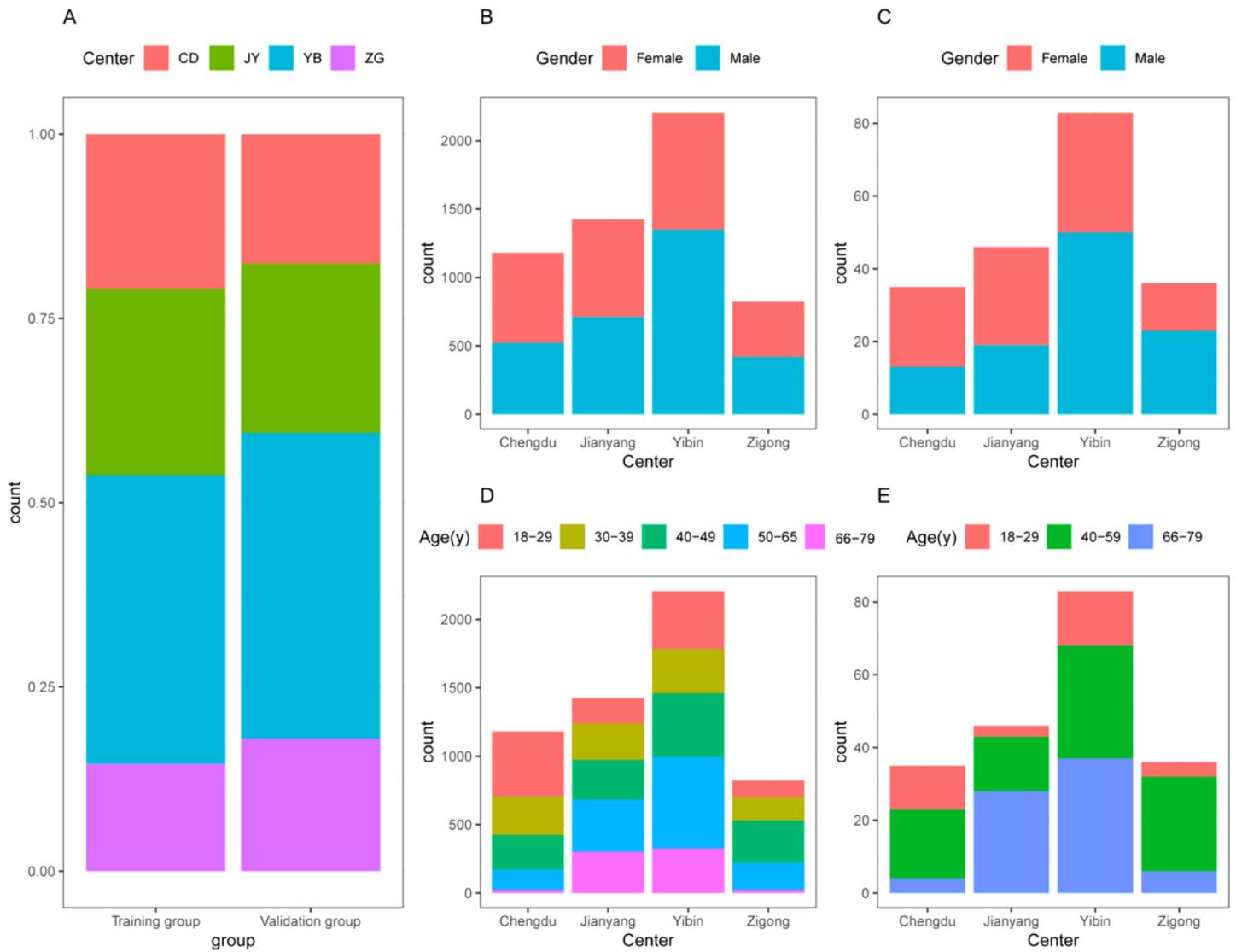


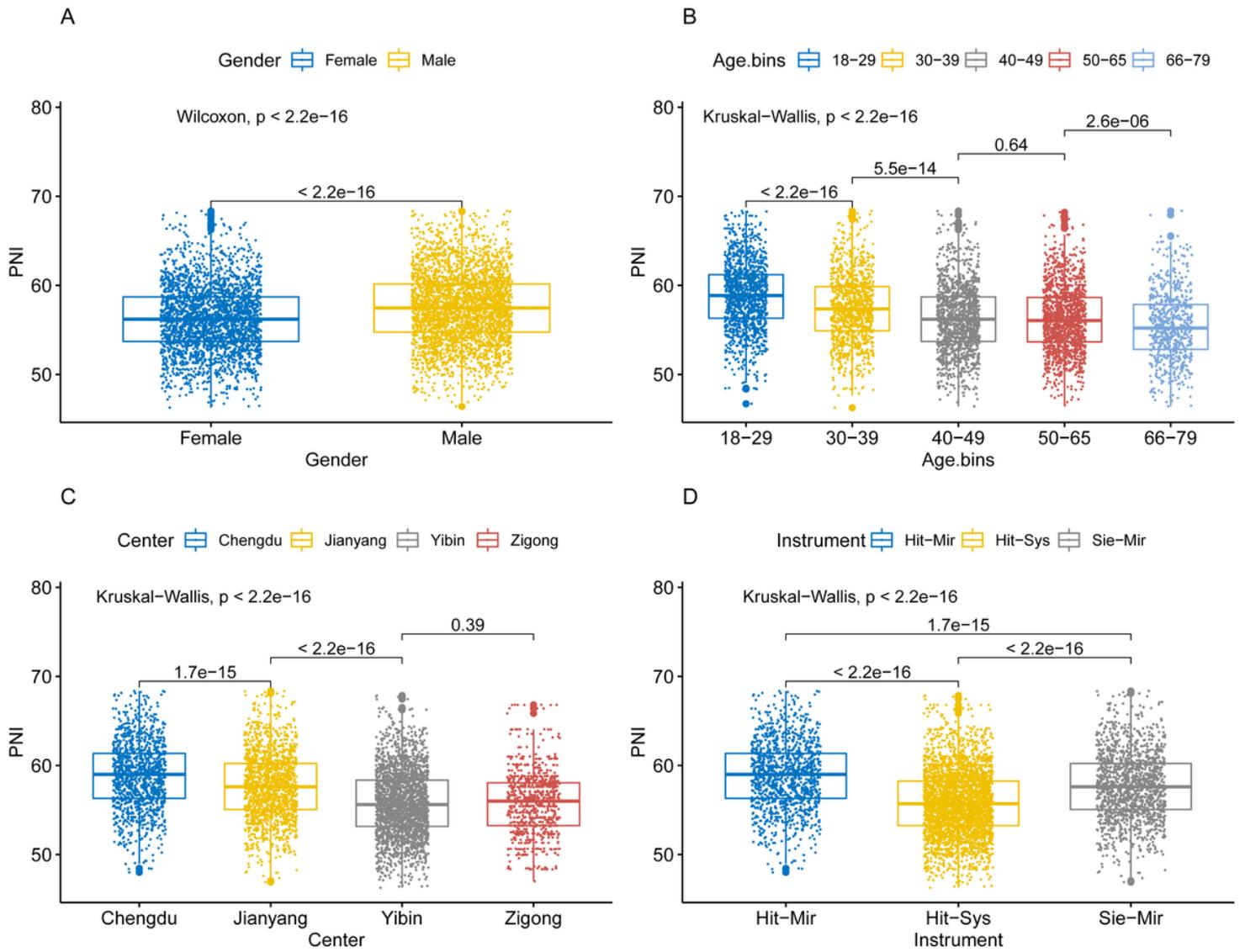
Figure 1

Flowchart of inclusion and exclusion of subjects to establish the reference intervals.



**Figure 2**

The distribution of candidates from each center, different genders and age groups in the training group and validation group.



**Figure 3**

The boxplot of PNI stratified by gender, age, center and instrument in training group. Our boxplot is not a standardized way and displays the distribution of data based on the three numbers summary: first quartile, median, third quartile.

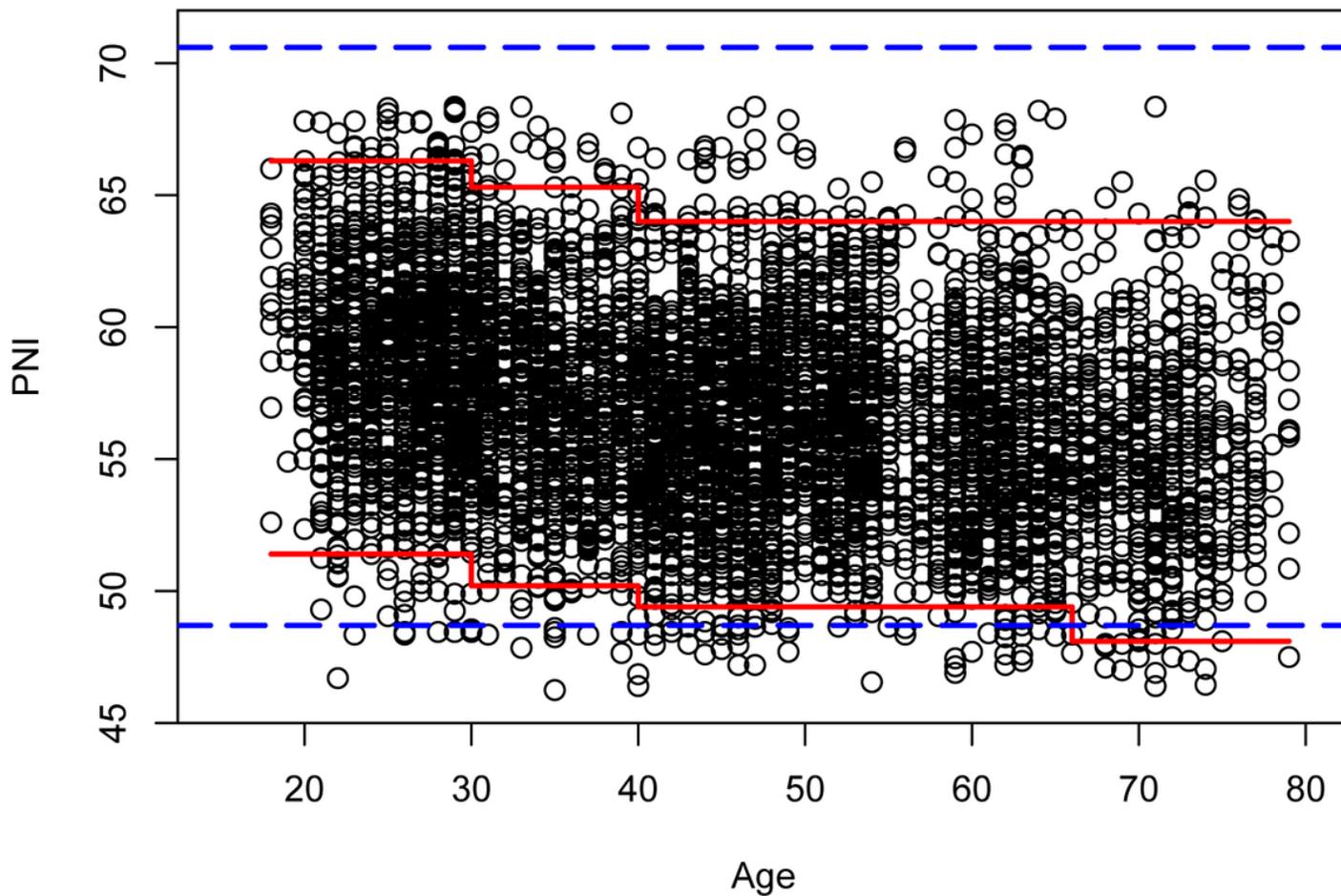


Figure 4

The scatter plot to show the association between PNI and age in training group. Partitioned intervals are shown with the red stepped line, and the existing unpartitioned interval is shown with the black dashed line. Individual points are shown as black circles.