# Hypoperfusion of amygdala in chronic migraine: an exploratory quantitative perfusion imaging using 3D pseudo-continuous arterial spin labeling

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## Abstract

**Background:** Amygdala, an essential element of the limbic system, has served as an important structure in pain modulation. Although previous studies have described the structural and functional abnormalities of amygdala in chronic migraine (CM), less is known about the altered perfusion. The study aimed to measure amygdala perfusion in CM with a contrast agent-free and quantitative approach.

**Methods:** Thirteen CM patients and 15 normal controls were enrolled in the examination, and were performed with conventional brain structural imaging sequences and 3D pseudo-continuous arterial spin labeling (3D-PCASL). The amygdala was used as a seed region to extract volume and cerebral blood flow (CBF) value of all subjects. The correlation analysis and receiver operating characteristic curve (ROC) were used to observe the perfusion changes and explore underlying mechanism of neurolimbic pain-modulation in CM.

**Results:** Decreased cerebral perfusion of bilateral amygdala was identified in CM (left amygdala, 42.21±4.49 ml/100mg/min; right amygdala, 42.38±4.41 ml/100mg/min) compared with NC (left amygdala, 48.31±6.92 ml/100mg/min; right amygdala, 47.88±6.53 ml/100mg/min). There was no any significant correlation between the perfusion of bilateral amygdala and the clinical variables. And there was no significant difference for the bilateral amygdala volume between two groups. The area under curve (AUC) for the CBF value of left and right amygdala were 0.78 (95%CI 0.58-0.91) and 0.75 (95%CI 0.55-0.89), respectively. The cut-off value was 44.24 ml/100mg/min (left amygdala, with sensitivity 76.90% and specificity 78.70%) and 46.75 ml/100mg/min (right amygdala, with sensitivity 92.3% and specificity 58.80%).

**Conclusion:** CM presented hypoperfusion in bilateral amygdala, which had potential diagnostic efficacy in discriminating CM from NC. The 3D-PCASL could be considered as a simple and effective tool to identify the perfusion status in migraine.


## Introduction

Migraine is a neurovascular brain disorder characterized by recurrent attacks of moderate to severe in intensity, and often accompanied with temporary autonomic nervous system dysfunction[1]. According to International Classification of Headache Disorders, 3rd edition (ICHD-III), chronic migraine (≥ 15 days more than 3 months) has the features of typical headache at least eight days a month[2]. The prevalence of chronic migraine (CM) is 1–2% of general population, with approximately 2.5% of persons with episodic migraine (EM) evolving to CM[3]. As the sixth greatest cause of disability worldwide[4], however, question concerning the neuromechanism of the migraine, which would help to early diagnose and better treatment to improve the life quality of patients, is remaining elucidated.

Among the advanced studies probing into the mechanism, it is widely accepted that migraine pathophysiology involved in recurrent activation and sensitization of the trigeminovascular pathway[5]. Currently, cortical spreading depression (CSD) has been proposed as the underlying mechanism of aura[6]. A behavioral study in experimental animals found that a single episode of CSD was unlikely to lead to severe pain in freely moving rats, and CSD induced freezing behavior by invoking fear and anxiety via amygdala activation[7].

Amygdala, an essential element of the limbic system, has emerged as an important brain structure for the emotional-affective dimension of pain and pain modulation[8]. Therefore, the amygdala dysfunction may help bridge a gap in understanding the chronicization pathophysiology of migraine pain[9]. Previous studies have described structural and functional changes of amygdala in migraineurs, including as follows: (1) smaller volume in CM patients compared with EM[10]; (2) increased neural activity in response to negative emotional stimuli[11]; (3) the aberrant connectivity to pain-related regions[12–14]. Considerable progress has been made in elucidating the pathophysiology of amygdala in migraine, however, most previous studies omitted status of the perfusion, which was coupled to changes in metabolism and worth paying close attention.

Modern neuroimaging techniques have produced a significant advance in our knowledge about tissue perfusion. Three-dimensional pseudo-continuous arterial spin labeling (3D-PCASL) is a non-invasive magnetic resonance imaging (MRI) technique that can quantitatively measure cerebral blood flow (CBF) with the advantage of repeatability and the avoidance of intravenous contrast administration[15]. ASL can be carried out in the diagnosis and management of acute stroke, arteriovenous malformations, neoplastic disease et al[16]. However, less is known about the study of amygdala using ASL technique.

To address this issue, we would apply 3D-PCASL to identify differences in amygdala perfusion between CM patients in the interictal stage and normal controls (NCs). We selected the amygdala as a template to observe the perfusion and volume changes, and explore underlying mechanism of neurolimbic pain-modulation in CM. We hypothesized that the perfusion and volume of amygdala would be influenced by migraine and the alteration would be associated with clinic characteristics. Moreover, receiver operating characteristic (ROC) curve analysis was performed to estimate the diagnostic efficacy of amygdala perfusion for CM distinguishing from NC.

# Methods

### Subjects

Twenty-eight subjects were sequentially enrolled, including 13 CM patients from the headache clinic and 15 normal controls (NC) from the hospital staffs or their relatives. The inclusion criteria were based on the International Classification of Headache Disorders, third Edition (beta version) (ICHD -3 beta)[17], including as following: (1) the diagnosis of migraine refers to 1.1 Migraine without aura and CM refers to 1.3 in ICHD-III, respectively; (2) without migraine preventive medication in the past 3months; (3) absence of other subtypes of headache, chronic pain other than headache, severe anxiety or depression, and psychiatric diseases; (4) absence of alcohol, nicotine, or other substance abuse; (5) right-handed; (6) no cerebral infarction, malacia or occupying lesions on the conventional MRI. The exclusion criteria were listed as the following: cranium trauma, the cerebrovascular disease, chronic disorders such as hypertension, diabetes mellitus, and coronary heart disease etc. All the subjects should have no MRI contraindications such as metal clips within the body and claustrophobia.

All the CM patients received Visual Analogue Scale (VAS) and Migraine Disability Assessment (MIDAS) evaluation, and all the subjects underwent the following neuropsychological scale: Hamilton Anxiety Scale (HAMA), Hamilton Depression Scale (HAMD) and Montreal Cognitive Assessment (MoCA). MRI examination was performed in the headache-free period for the CM patients, and the alcohol, nicotine, caffeine and other substances were avoided at least 12 hours before MRI examination. Written informed consent was obtained from all participants according to the approval of the ethics committee.

### MR imaging

All the MR data was obtained from a GE 3.0T MR scanner (DISCOVERY MR750, GE Healthcare, Milwaukee, WI, USA), and a conventional eight-channel quadrature head coil was used to acquire the image. The MR protocals included as follows: (1) axial three-dimensional T1-weighted fast spoiled gradient recalled echo (3D T1-FSPGR) sequence generating 360 slices: repetition time (TR) = 7.0 ms, echo time (TE) = 3.0 ms, flip angle = 15 , field of view (FOV) = 25.6 cm×25.6 cm, Matrix = 256×256, slice thickness = 1mm, number of acquisition = 1; (2) axial pseudo-continuous arterial spinal labelling (ASL) tagging scheme with a 3D interleaved spiral fast spinal echo (FSE) readout (3D spiral FSE ASL) generating 50 CBF slices: TR/TE = 5128 ms/15.9 ms, flip angle = 111 , FOV= 20cm×20cm, x, y matrix = 1024 × 8 (spiral acquisition), slice thickness = 3.0 mm, labeling duration was 1.5 s, and post-labeling delay time (PLD) was 1.5 s. The conventional oblique T2 weighted imaging (T2WI), diffusion weighted imaging (DWI) and T2 fluid attenuated inversion recovery (T2-FLAIR) were performed to exclude the subjects with obvious brain lesions. All the subjects received the same MR protocals in the interictal stage.

### Image processing

All MR data was processed using Statistical Parametric Mapping 12 (SPM 12) and computational anatomy toolbox (CAT12) plugin (http://www.fil.ion.ucl.ac.uk/spm/) running under MATLAB 7.6 (The Mathworks, Natick, MA, USA). The image processing included following steps (Figure 1): (1) The structural image (3D T1-FSPGR) were segmented using CAT12 tool and generated inverse deformation field (IDF); (2) The IDF was applied with amygdala templated obtaining from the Neuromorphometrics template (http://neuromorphometrics.com/), which would generate individual amygdala mask; (3) The CBF image was coregistered with raw T1 image (3D) and generated resliced CBF imaged (rCBF) ; (4) The CBF value of amygdala was extracted from the rCBF based on the individual amygdala mask, and the volume of amygdala was also extracted from the raw 3D T1-FSPGR based on the individual amygdala mask.

### Statistical analysis

The statistical analysis was performed by using MedCalc (V19.0.4). The data with non-normal distribution presented by median (minimum, maximum) and the data with normal distribution presented as mean ± standard deviation. The clinical variables, including age, HAMA, HAMD, MoCA and CBF value, were performed with independent sample *t* test. The qualitative variable gender was performed with Chi-Square test. The Pearson correlation was performed with the data with normal distribution, and the Spearman correlation was performed with the data with non-normal distribution. A *p* value less than 0.05 was considered indicative of statistical significance.

ROC curve analysis was performed to identify the diagnostic efficacy of amygdala perfusion for CM, and area under the curve (AUC) was recognized reasonable diagnostic valuable with AUC set at >0.7.

# Results

### Demography and neuropsychological test

The current study included 13 CM patients and 15 NCs. The clinical information was listed in the table 1. The age and gender showed no significant difference between two groups (*p* value was 0.44 and 0.1, respectively). The HAMA score presented significant difference between CM (22.30±12.05) and NC (9.73±3.39) (p value of < 0.001), while HAMD and MoCA score showed no significant difference between two groups.

### Comparison of the amygdala perfusion and volume between CM and NC

Table 2 presented that the significant decreased cerebral perfusion of bilateral amygdala was identified in CM (left amygdala, 42.21±4.49 ml/100mg/min; right amygdala, 42.38±4.41 ml/100mg/min) compared with NC (left amygdala, 48.31±6.92 ml/100mg/min; right amygdala, 47.88±6.53 ml/100mg/min) (left, $p = 0.01$; right, $p = 0.02$) (Figure 2). But there was no any correlation between the CBF value of bilateral amygdala and the clinical variables ($p > 0.05$).

There was no significant difference for the bilateral amygdala volume in CM (left: 0.53±0.05ml, right: 0.86±0.08ml) compared with NC (left: 0.55±0.08ml, right: 0.86±0.11 ml) (left: $p = 0.83$, right: $p = 0.14$).

### ROC analysis of the amygdala perfusion between CM and NC

The AUC for the CBF value of left and right amygdala were 0.78 (95%CI 0.58-0.91) and 0.75 (95%CI 0.55-0.89), respectively (Table 2 and Figure 3). The cut-off value was 44.24 ml/100mg/min (left amygdala, with sensitivity 76.90% and specificity 78.70%) and 46.75 ml/100mg/min (right amygdala, with sensitivity 92.3% and specificity 58.80%).

# Discussion

In the present study, bilateral amygdala perfusion presented significant decreased cerebral perfusion, but the alteration was not correlated with the clinical variables. Then, there was no significant difference for the bilateral amygdala volume between two groups. In addition, the ROC analysis showed that 3D-PCASL had moderate diagnostic efficacy in discrimination.

Altered interictal perfusion of amygdala may reflect differences in neuronal activity or density, in other words accompanying with structural and functional changes. A voxel-based morphometry (VBM) analysis showed CM patients presented a significant volume reduction in the amygdala compared with EM[10], differing from the increased volume with chronic low back pain[18]. Another study demonstrated that the amygdala volume changed structurally with headache frequency, and correlated with frequency in specific ranges[19], while the headache frequency and disease duration equally had influence on CBF[20]. This could be the consequence of repetitive migraine attacks or chronic adaptive mechanisms, leading the volume and perfusion changes of amygdala, which implied a possible damage or degeneration of neurons. Thus, the current study suggested that the decreased perfusion might be another proof of structural damage and attributed to neuroplasticity induced by pain. Mesnwhlie, this study measured the volume of amygdala at the same time, finding there was no siginificant difference between two groups. Therefore, the perfusion change happened prior to the volume alternation, which could supply another clue to definite the possible relationship: whether decreased perfusion was the trigger or consequence of volume alteration, or a bidirectional relationship between them.

Hemodynamic changes could identify the pain perception process, and multiple brain regions both responded to pain and participated in pain control in the process[21]. The abnormal functional connectivity may be the direct manifestation of pain perception process in migraine from the viewpoint of blood oxygen level dependent (BOLD) effect in resting state. Some studies have proved that migraine is associated with changes in functional connectivity between different regions[12–14, 22] as following: (1) a significantly decreased effective connectivity from the right amygdala to bilateral superior temporal gyrus, right inferior occipital lobe, while enhanced from left inferior frontal gyrus to left amygdale; (2) increased connectivity of amygdala in migraineurs was observed to the visceroceptive cortex. Therefore, it could be speculated that the altered functional connectivity (BOLD effect) might be associated with the perfusion change in amygdala in CM, which also indicated that it should be performed with the functional connectivity and 3D-PCASL study simultaneously to construct neurovascular coupling (NVC) model for amygdala in the future migraine research[23].

Previous perfusion studies, using single photon emission computed tomography (SPECT) or PET, reported contradicting results about cerebral hemodynamics. Migraine patients presented a normal cerebral blood flow pattern during migraine attacks[24], which was conflict with the interictal hypoperfusion of single or multiple brain regions in migraineurs [25] and interictal global hyperperfusion mainly locating in frontal regions in migraine without aura[26]. These inconsistent results might be partly associated with the unreliability of visual evaluation of data acquisition from SPECT CBF images[27]. Subsequently, dynamic susceptibility contrast-perfusion weighted imaging (DSC-PWI) study identified areas of hypoperfusion more than one vascular territory in patients with migraine with aura[28]. Besides these, the prior study using dynamic contrast material–enhanced (DCE) MRI with a voxel-wise whole brain comparison showed interictal migraineurs had discrete areas of cerebral hyperperfusion and hypoperfusion[20]. Another DCE-MRI research quantified blood-brain barrier (BBB) permeability in migraine, observing the mean fractional plasma volume in the left amygdala was lower in the migraine group[29]. This finding was consistent with the decreased perfusion of the current results to some degree although the relationship between BBB integrity and metabolic changes in migraine cannot be directly correlated[29]. The discrepancy in perfusion status may be associated with the spatial heterogeneity of CBF changes during migraine[30]. And the comparison between these complicated techniques remained unsubstantiated because of differences in post-processing.

Abnormal regional cerebral hyperperfusion was associated with migraine headache using ASL in hemiplegic migraine patient and EM[31], while bilateral amygdala was coupled with hypoperfusion in CM in this study. The discrepancy in the cerebral perfusion status might signal the chronicization of migraine at hemodynamics level and further provide a novel view to the mechanisms of initiation, continuation, and termination of migraine.

Alterations in amygdala that modulated the pain in migraine suggested a possible neurobiological mechanism, which may explain the link between CM and psychiatric disturbances. This study found CM patients were more susceptible of anxiety in accordance with earlier finding[32], while there was no any significant correlation between the CBF value of amygdala with clinical variables including HAMA assessing anxiety. However, earlier findings reported the associations between migraine and stress, anxiety and depression[33–35]. Therefore, CBF value would be an independent factor in CM, but the possibility relationship between pathophysiologic mechanism and perfusion alteration should be discussed further.

Figure 3 presented perfusion of bilateral amygdala with moderate discrimination for the diagnosis of CM with the AUC of 0.78 (95% CI 0.58–0.91) and 0.75 (95% CI 0.55–0.89) for the left and right amygdala, respectively. Note that the AUC describes the test's ability to discriminate between subjects with and without the condition[36]. The current study could confirm that the decreased perfusion of amygdala is more common in CM than that in NC in the about 75% -78% of comparisons from the statistical viewpoint. Therefore, the CBF value could be a potential imaging biomarker for the diagnosis of CM with objective and comprehensive considerations.

The 3D-PCASL analysis in the current study was applied with more advanced acquisition and post-processing technique than traditional methods. Compared with SPECT and PET, 3D-PCASL does not expose the subjects to ionizing radiation and has the possibility for repeated measurements to increase the sensitivity. On the other hand, one study had proposed 3D-PCASL methodology may provide an alternative to PET that can be obtained during routine MRI in clinical practice and research[37]. Instead of DSC-MRI exogenous contrast agent, 3D-PCASL is based on the endogenous blood-based water in the arteries itself, therefore, has the superiority of avoiding the risk of drug allergy[38]. Meanwhile, 3D-PCASL can break through the limitations of traditional 2D-ASL, accelerate the acquisition time and produce quantitative images of perfusion[37, 38]. Therefore, 3D-PCASL technique could be considered as a simple and effective tool to evaluate the perfusion status of amygdala in migraine research.

Limitations of this study included as follows: (1) the sample size was relatively small, and the further ASL studies are required larger-population to reflect the neuromechanism of CM; (2) this study only presented the perfusion changes in the interictal stage, future studies should assess different (interictal and ictal) timepoints in the migraine cycle to evaluate the reproducibility of 3D-pASL; (3) our study relied on cross-sectional data rather than longitudinal data, therefore, the exact causal relationship between amygdala perfusion and migraine chronicization could not be determined.

# Conclusion

In conclusion, significant hypoperfusion of bilateral amygdala was identified in the current study with 3D-pASL technique in CM. The non-invasive 3D-PCASL technique had moderate diagnostic efficacy in discriminating CM from NC, which could be considered as a quantitative and effective tool to detect the brain perfusion in migraine neuroimaging.

# Abbreviations

CM, Chronic migraine; EM, episodic migraine; NC: normal control; 3D-PCASL, 3D pseudo-continuous arterial spin labeling; CBF, cerebral blood flow; CSD, cortical spreading depression; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale; MoCA, Montreal Cognitive Assessment; VAS, Visual Analog Scale; MIDAS, Migraine Disability Assessment Scale; DD, disease duration; NA, Not available; DD, disease duration; HDPM, headache days per month; FDR, false discovery rate; ROC, receiver operating characteristics; AUC, area under curve.

# Declarations

### Ethic approval and consent to participate

The Institutional Review Board of the Chinese PLA General Hospital approved the research protocol, and the procedures conformed to the tenets of the Declaration of Helsinki. And all subjects had been informed of the relevant benefits and risks before being examined, and the subjects agreed to participate in the study and signed an informed consent.

### Consent for publication

Not applicable

### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Competing interests

The authors declare that they have no competing interests.

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### Authors' contributions

ZYC designed of the work and performed data analysis, statistical analysis. He also acted as study supervisor. XL drafted and revised the work and data interpretation, and was a major contributor in writing the manuscript. MQL acquired data and analyzed the patient data. All authors read and approved the final manuscript.

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### Footnotes

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# Tables

Table 1

The clinical characteristics of CM and NC

| | Age(years) | Gender(F/M) | DD(years) | VAS | HAMA | HAMD | MoCA | MIDAS |
|---|---|---|---|---|---|---|---|---|
| **CM** | 40.69±8.60 | 9/4 | 8(3,30)[b] | 7.77±1.36 | 22.30±12.05 | 16.46±10.58 | 23.38±4.98 | 102.62±47.53 |
| **NC** | 38.00±9.56 | 11/4 | NA | NA | 9.73±3.39 | 15.73±2.91 | 26.47±2.42 | NA |
| ***t* value** | 0.78 | 1.02[a] | | | 3.64[c] | 0.24[c] | 2.04[c] | |
| ***p* value** | 0.44 | 0.31 | | | 0.00 | 0.81 | 0.06 | |

[a]$\chi^2$ value; [b]Median(minimum value, maximum value); [c]Welch test (unequal variances); NA, not available; DD, disease duration; VAS, Visual Analog Scale; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale; MoCA, Montreal Cognitive Assessment; MIDAS, Migraine Disability Assessment Scale.

Table 2

Comparison and ROC analysis of the amygdala perfusion between CM and NC

| | Group | CBF value[a] | *t* value | *p* value | AUC(95%CI)[b] | Cut-off value[a] | Sensitivity | Specificity |
|---|---|---|---|---|---|---|---|---|
| **Left** | | | | | | | | |
| | CM | 42.21±4.49 | 2.72 | 0.01 | 0.78(0.58-0.91) | 44.24 | 76.90% | 78.70% |
| | NC | 48.31±6.92 | | | | | | |
| **Right** | | | | | | | | |
| | CM | 42.38±4.41 | 2.57 | 0.02 | 0.75(0.55-0.89) | 46.75 | 92.30% | 58.80% |
| | NC | 47.88±6.53 | | | | | | |

[a]ml/100mg/min; CM, chronic migraine; NC, normal control; CBF, cerebral blood flow; AUC, the area under receiver operating characteristic curve; CI, confidence interval

## Figures

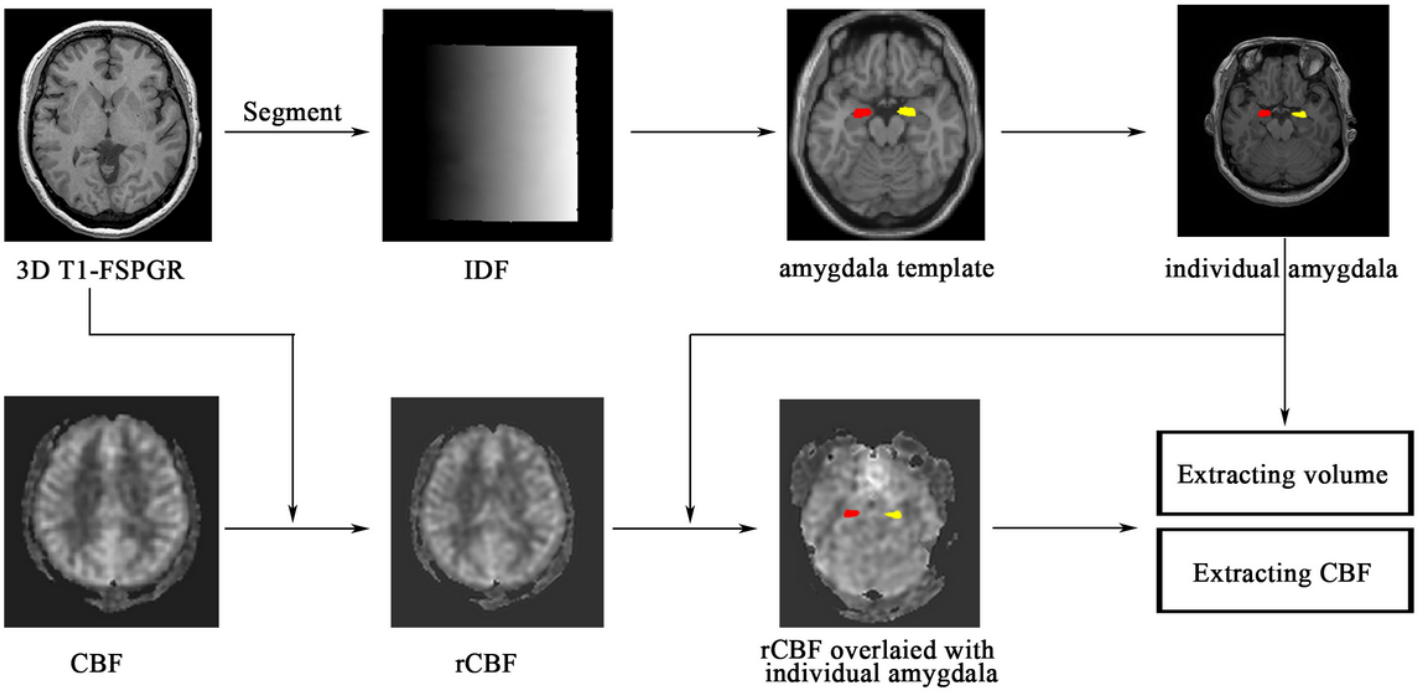


Figure 1

Legend not included with this version

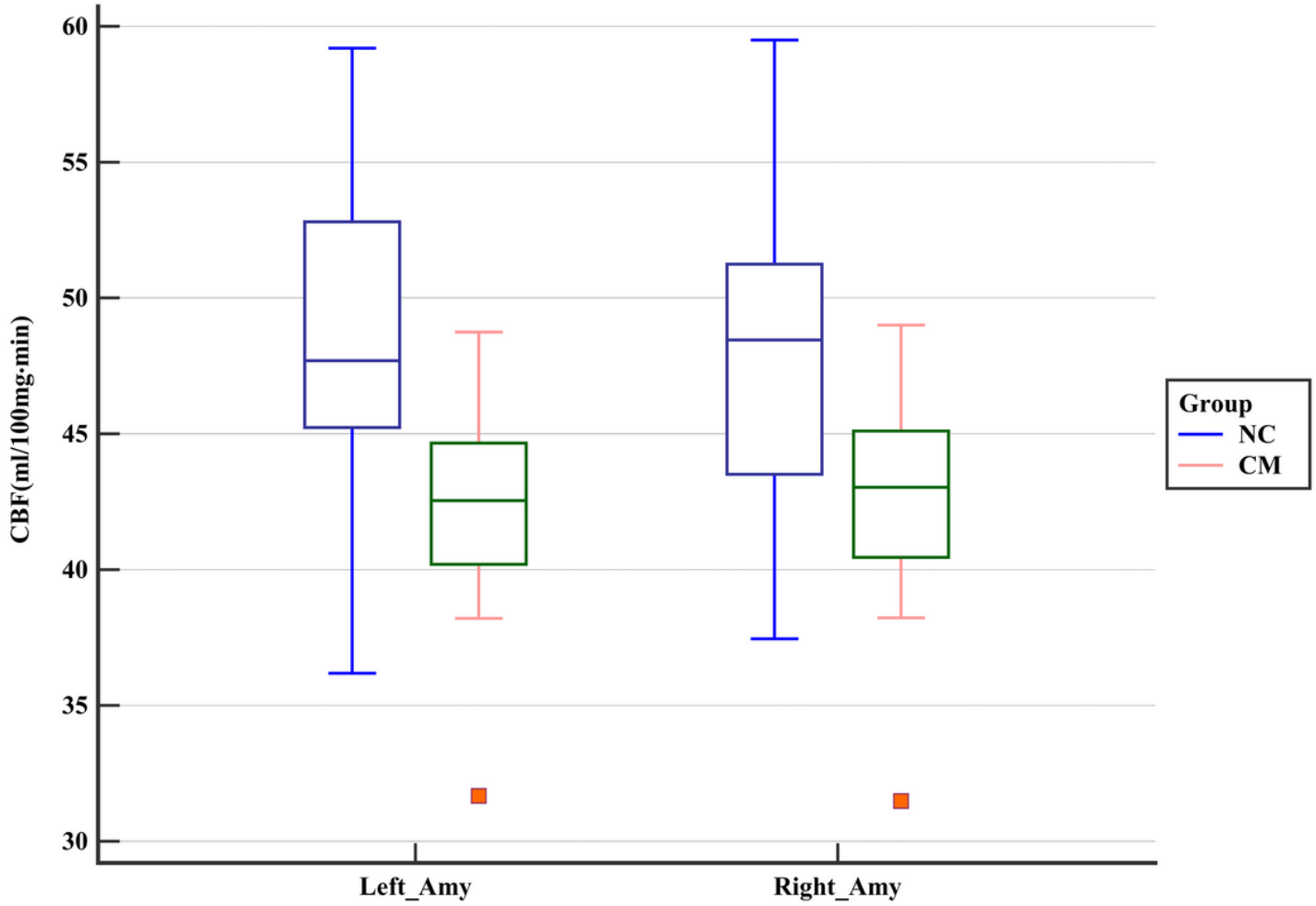

**Figure 2**

Legend not included with this version

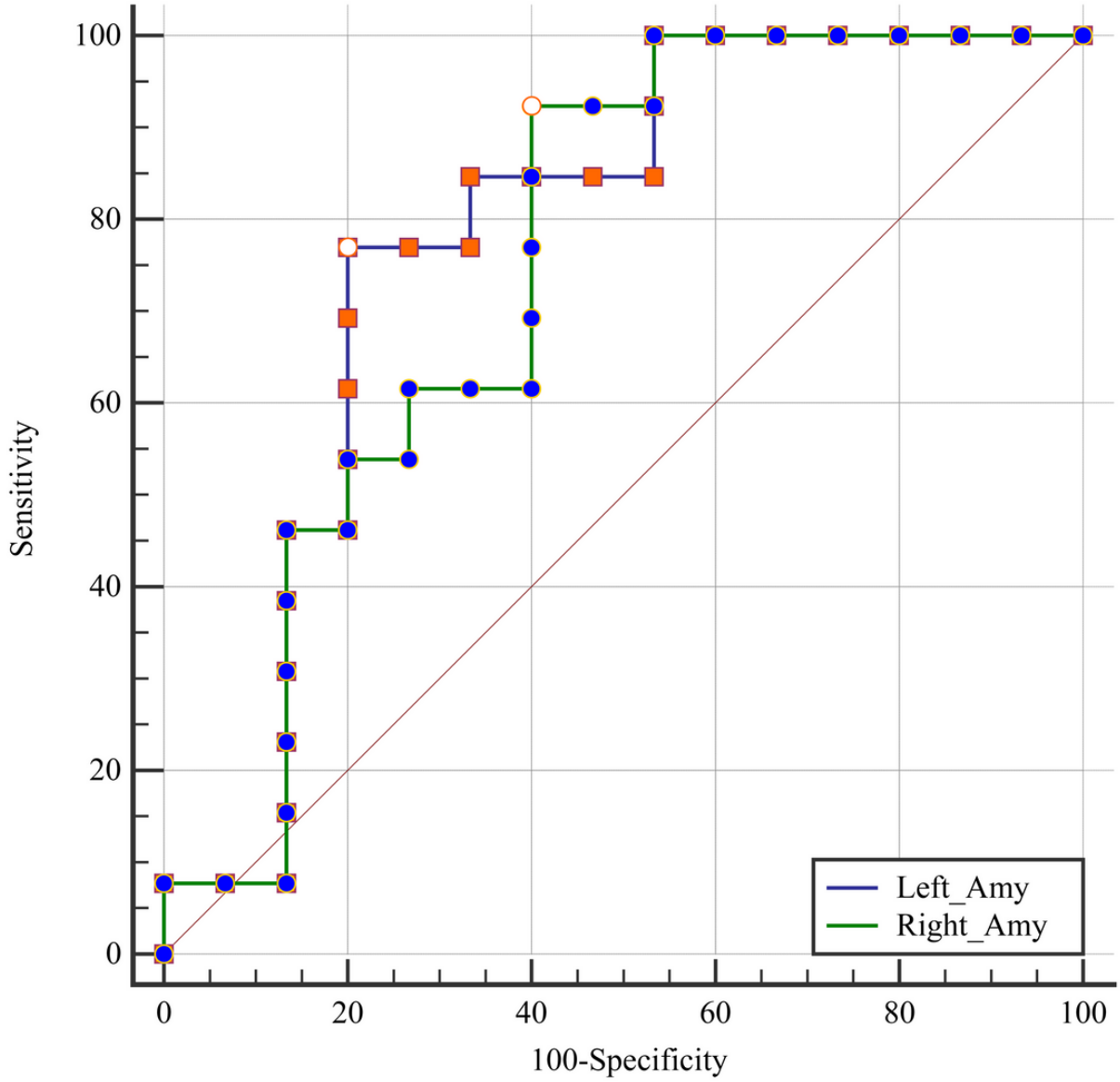


**Figure 3**

Legend not included with this version