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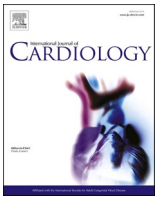

Geographic disparity of pathophysiological coronary artery disease characteristics: Insights from ASET trials

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ABSTRACT

Background: The geographical disparity in the pathophysiological pattern of coronary artery disease (CAD) among patients undergoing percutaneous coronary intervention (PCI) is unknown.
Objectives: To elucidate the geographical variance in the pathophysiological characteristics of CAD.
Methods: Physiological indices derived from angiography-based fractional flow reserve pullbacks from patients with chronic coronary syndrome enrolled in the ASET Japan ($n = 206$) and ASET Brazil ($n = 201$) studies, which shared the same eligibility criteria, were analysed.

Abbreviations: CAD, coronary artery disease; dμQFR/ds, μQFR gradient per mm; FFR, fractional flow reserve; PCI, percutaneous coronary intervention; PPG, pullback pressure gradient; μQFR, Murray law-based quantitative flow ratio.

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The pathophysiological patterns of CAD were characterised using Murray law-based quantitative flow ratio (μQFR)-derived indices acquired from pre-PCI angiograms. The diffuseness of CAD was defined by the μQFR pullback pressure gradient index.

Results: Significant functional stenoses pre-PCI (μQFR ≤0.80) were more frequent in ASET Japan compared to ASET Brazil (89.9% vs. 67.5%, $p < 0.001$), as were rates of a post-PCI μQFR <0.91 (22.1% vs. 12.9%, $p = 0.013$). In the multivariable analysis, pre-procedural μQFR and diffuse disease were independent factors for predicting a post-PCI μQFR <0.91, which contributed to the different rates of post-PCI μQFR ≥0.91 between the studies. Among vessels with a post-PCI μQFR <0.91, a consistent diffuse pattern of CAD pre- and post-PCI occurred in 78.3% and 76.7% of patients in ASET Japan and Brazil, respectively; only 6.3% (Japan) and 10.0% (Brazil) of vessels had a major residual gradient. Independent risk factors for diffuse disease were diabetes mellitus in ASET Japan, and age and male gender in Brazil.

Conclusions: There was geographic disparity in pre-procedural angiography-based pathophysiological characteristics. The combined pre-procedural physiological assessment of vessel μQFR and diffuseness of CAD may potentially identify patients who will benefit most from PCI.

1. Introduction

Cardiovascular disease remains a major cause of mortality worldwide, however there is a geographic disparity in its prevalence, treatment and management strategies for modifiable, non-genetic risk factors [1]. Among the five primary risk factors for coronary artery disease (CAD)—hypertension, hyperlipidaemia, obesity, smoking, and diabetes mellitus—diabetes mellitus poses a greater burden in Asia, while the other four are more prevalent in Europe and Central Asia compared to other regions of the world [2].

In Japan, patients undergoing percutaneous coronary intervention (PCI) are typically older and have higher rates of diabetes, hypertension, and complex lesions compared to those in Europe [3,4]. Moreover, the j-Cypher and Bern-Rotterdam registries revealed lower mortality and stent thrombosis rates in the Japanese cohort at five years [3]. In contrast, Kohsaka et al. reported that, compared to patients undergoing revascularisation in Japan, those in the United States presented with higher obesity rates and frequency of previous atherosclerosis-related events such as myocardial infarction, peripheral vascular disease, renal insufficiency, and hypertension [5]. Understanding the geographic (and ethnic) disparities in cardiovascular disease and risk factors could support the development of effective prevention efforts since each population epitomises diverse political histories and a variety of social, economic, and cultural backgrounds that can influence cardiovascular health in different ways [6].

The advent of angiography-based fractional flow reserve (FFR) has advanced the functional assessment of coronary stenoses by eliminating the need for wire and hyperemic agents, thus reducing procedural time and patient discomfort compared to conventional intracoronary pressure measurements [7]. Angiography-based FFR allows the generation of a virtual pullback curve and characterisation of pathophysiological patterns of CAD as well as discrimination of the physiological contribution of every single lesion [8]. Recent studies highlight the role of preprocedural pathophysiological CAD patterns, characterised by the magnitude and distribution of the pressure drop along the target vessel using wire-based or angiography-based FFR pullback pressure gradients, in predicting the physiological response to PCI and subsequent clinical outcomes [9–15].

While earlier investigations have identified disparities in atherosclerosis risk factors and baseline clinical and lesion characteristics across diverse geographical populations, the potential variation in pathophysiological patterns of epicardial CAD among those undergoing contemporary PCI remains unexplored. We hypothesised that geographical variance in pathophysiological patterns of CAD, as well as in baseline clinical characteristics, might exist between patients undergoing PCI in the Far East and South America. To test this hypothesis, we pooled and compared physiological indices derived from angiography-based FFR virtual pullbacks of patients enrolled in the ASET Japan and ASET Brazil studies, which both shared the same eligibility criteria.

2. Methods

2.1. Study population

This study included 206 and 201 consecutive patients with chronic coronary syndrome (CCS) enrolled in the ASET (Acetyl Salicylic Elimination Trial) Japan (NCT05117866) and the ASET Brazil study (NCT03469856), respectively.

The study design and results were previously reported [16–19]. Briefly, both studies are multi-centre, single-arm, open-label, proof-of-concept trials—with a stopping rule based on the occurrence of definite stent thrombosis—that demonstrated the feasibility and safety of "aspirin-free" therapy with prasugrel monotherapy following PCI in Japanese and Brazilian population with CCS, respectively.

These two studies shared the same eligibility criteria with different dosages of Prasugrel according to local regulatory approval. The inclusion and exclusion criteria have been previously reported [16,19]. Briefly, in both studies, patients requiring PCI for CCS who had an anatomical SYNTAX score < 23 were screened and considered for enrolment. Only patients with optimal stent implantation based on the local standard of care (i.e., angiography, quantitative coronary angiography [QCA], intracoronary imaging assessment) were enrolled.

The studies were approved by the certified review boards at the Fujita Health University (CRB4180003) and Comissão de Ética Para Análise de Projetos de Pesquisa (CAAE 77612017.0.1001.0068.), respectively, and the local ethics committees at each investigating centre. All patients provided their written informed consent prior to participation in the studies.

2.2. Analysis of angiography-derived FFR

The independent core laboratory (CORRIB Core Lab, Galway, Ireland) retrospectively performed the Murray law-based QFR (μQFR) analysis using AngioPlus Core software (version V2, Pulse Medical, Shanghai, China). μQFR is a novel computational method derived from a single angiographic view that incorporates ostial side branch diameters into the computation of fractal flow division [20–25]. Methods to compute μQFR are described in Supplemental Method 1 [20,26]. Contrast flow velocity was automatically converted to hyperemic flow velocity, and pressure drop was calculated using fluid dynamics equations. [20]. Significant flow limitation pre-procedure was defined by a cut-off μQFR ≤0.80 [20], whilst an optimal physiological procedural result was defined as a post-PCI μQFR ≥0.91 [26].

Relative μQFR gain from PCI was evaluated by the percentage μQFR increase as follows: 100 × (post-PCI μQFR – pre-PCI μQFR)/pre-PCI μQFR [12,27].

2.3. Preprocedural pathophysiological characterisation of CAD

Pre-procedural pathophysiological distribution of coronary athero-

sclerosis (*"diffuseness or focality"*) was assessed using μQFR-derived pullback pressure gradient (PPG) index calculated as follows [9,12,13] (Fig. 1, Fig. 2):

$$\mu\text{QFR}-\text{derived PPG index} = \frac{\left\{\frac{\textit{Max PPG 20mm}}{\Delta\mu\textit{QFR vessel}} + \left(1 - \frac{\textit{Length with functional disease (mm)}}{\textit{Total vessel length (mm)}}\right)\right\}}{2}$$

Maximal PPG was defined as the maximum μQFR gradient over 20 mm, and *delta μQFR vessel* as 1-vessel μQFR. The *length with functional disease* was defined as the length, in millimetres, with μQFR drop ≥0.0015/mm [9]. The *total vessel length* was defined as the length of the entire interrogated vessel. The pre-procedural and post-procedural physiological distribution of coronary atherosclerosis was defined as predominantly diffuse or focal according to a μQFR-derived PPG index <0.78 or ≥0.78, respectively [12].

The pre-PCI physiological local severity of a lesion was assessed using the μQFR gradient per mm (dμQFR/ds)(Fig. 2), with a value ≥0.025/mm defining the presence of a *"major gradient"* [12].

2.4. Statistical analysis

Continuous variables are presented as mean and standard deviation (SD) or as median and interquartile range (IQR) depending on their distribution and are compared using the Student's *t*-test or Mann-Whitney *U* test. Categorical variables are described as percentages and compared using chi-square test or Fisher exact, as appropriate.

To predict the unadjusted and adjusted risks of a post-PCI μQFR <0.91 in the pooled populations of the ASET Japan and ASET Brazil, we used binary logistic regression models with age, sex, diabetes mellitus, pre-procedural μQFR, PPG index, dμQFR/ds, use of intracoronary imaging for stent optimisation, and study population (ASET Japan vs. Brazil).

To predict unadjusted and adjusted risks of a post-PCI μQFR <0.91 in each study population, we used binary logistic regression models with pre-procedural μQFR, PPG index, and dμQFR/ds, as continuous predictor variables.

To predict unadjusted and adjusted risks of physiological diffuse disease (pre-PCI PPG index <0.78), we used binary logistic regression models with age, sex, body mass index, current smoking, diabetes mellitus, hypertension, dyslipidemia, peripheral artery disease, chronic obstructive pulmonary artery disease, and renal insufficiency.

A 2-sided *p*-value <0.05 was considered statistically significant. All statistical analyses were performed using R version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS version 27.0 (IBM, Armonk, NY, USA).

3. Results

From February 2018 to May 2019, 201 patients with 235 vessels were enrolled in the ASET Brazil study from 9 centres in Brazil. From November 2020 to September 2022, 206 patients with 217 vessels were enrolled in the ASET Japan study from 12 centres in Japan.

Baseline clinical characteristics are shown in Table 1. Patients from Japan were significantly older, and the proportion of males was significantly higher than those from Brazil. A history of dyslipidemia and renal insufficiency were more common in Japanese compared to

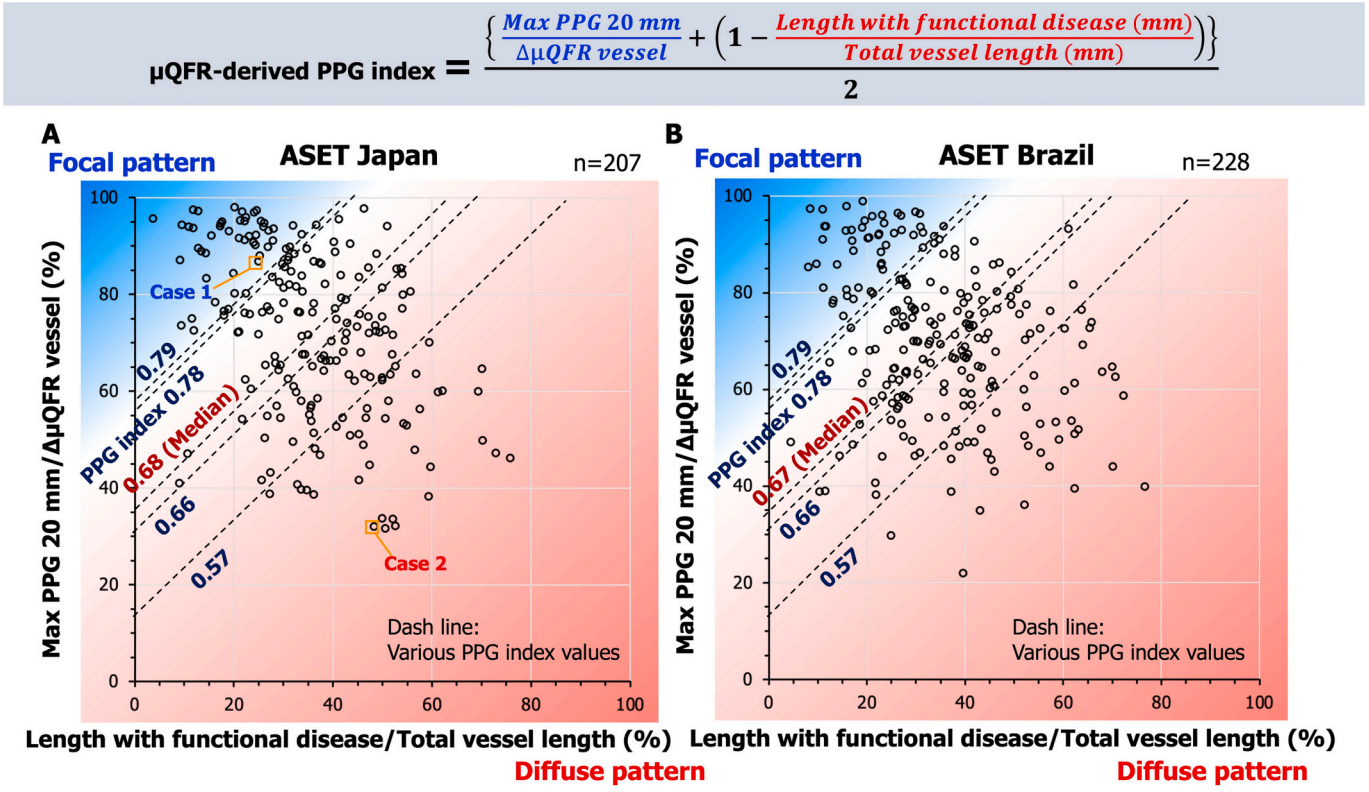

Fig. 1. Pre-procedural physiological distribution (*"diffuseness or focality"*) of coronary disease assessed using μQFR-derived PPG index in the ASET Japan (A) and ASET Brazil (B) studies.

In calculating the PPG index to assess the physiological distribution of coronary disease, the parameters of i) $\frac{\textit{Max PPG 20mm}}{\Delta\mu\textit{QFR vessel}}$ and ii) $\frac{\textit{Length with functional disease (mm)}}{\textit{Total vessel length (mm)}}$ contribute to focality and diffuseness, respectively. When the PPG index is constant, these two parameters are positively correlated with a slope of 1, which explains the various thresholds in the graphic diagram. The dashed lines show the threshold criteria of various median or mean PPG indexes: ASET Japan and ASET Brazil, median 0.68 vs. 0.67, respectively; PANDA III trial, median 0.79 [14]; Shin et al., median 0.78 [12]; TARGET-FFR and P3 study, median 0.66 [10,11]; and Collet et al., mean 0.57 [9]. PPG = pullback pressure gradient; μQFR = Murray law-based quantitative flow ratio.

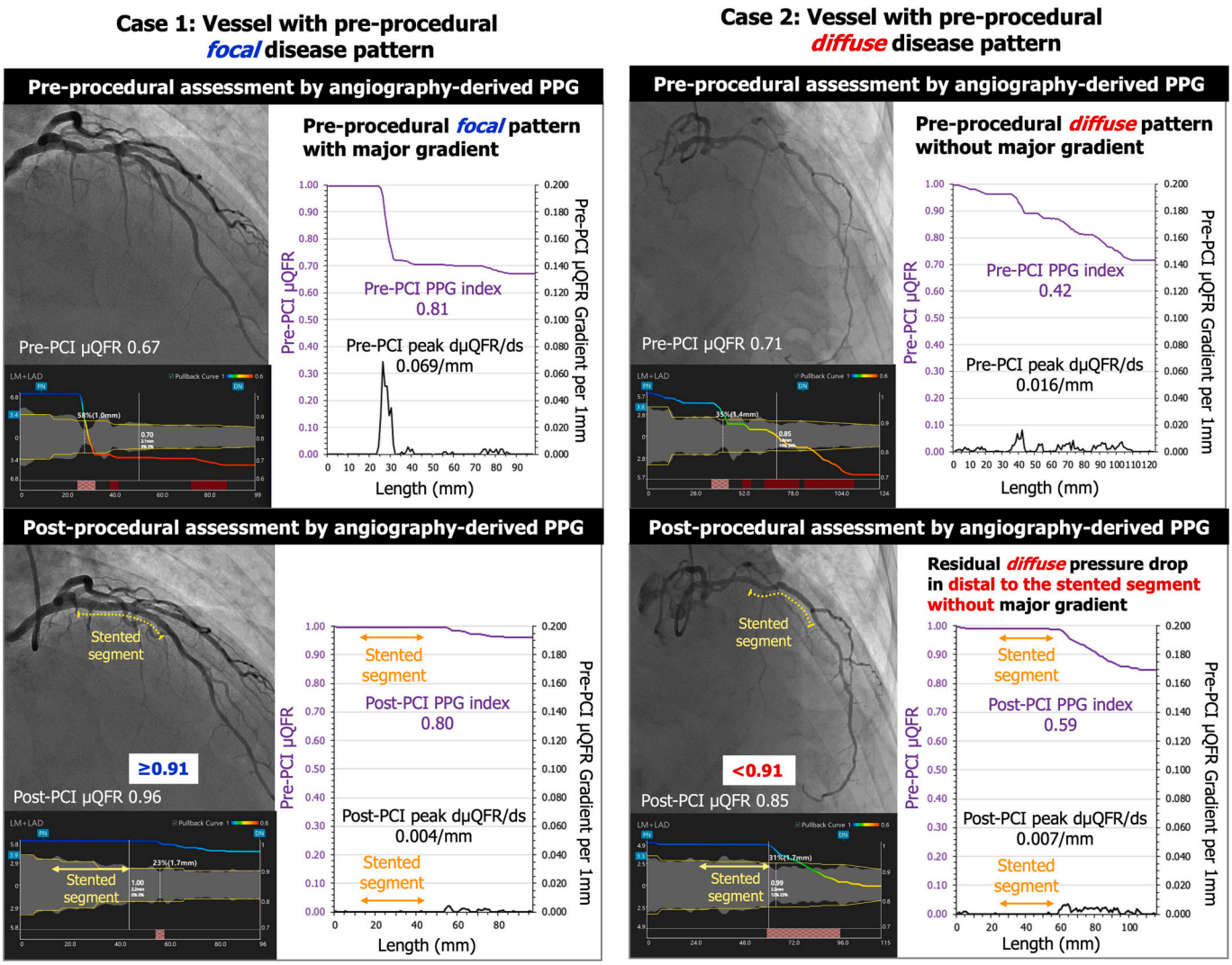

Fig. 2. Representative cases with pre-procedural focal (Case 1) and diffuse (Case 2) disease patterns.
Case 1 is a vessel which had a focal pattern of CAD pre-procedure (Pre-PCI PPG index ≥0.78) and a major gradient (pre-PCI dμQFR/ds ≥0.025/mm). The black curve in the graph shows the pressure gradient per mm (dμQFR/ds). The cumulative pressure drop is represented by the purple curve. Case 1 resulted in an optimal μQFR post-PCI.
Case 2 is a vessel which had a diffuse pattern of CAD pre-procedure (Pre-PCI PPG index <0.78) without a major gradient. Case 2 resulted in a sub-optimal post-PCI μQFR (<0.91). In this case, a residual peak dμQFR/ds was located distal to the stented segment with no major gradient (i.e., dμQFR/ds <0.025/mm), and a diffuse residual pressure drop was observed along the vessel distal to the stented segment with a post-PCI PPG index <0.78. PCI = percutaneous coronary intervention; PPG = pullback pressure gradient. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Brazilian population, whereas the opposite was observed for clinical characteristics such as hypertension and obesity. There was no significant difference in the anatomical SYNTAX score between the studies.

Lesion and procedural characteristics are shown in Supplemental Table 1. The number of patients with more than one treated lesion, as well as the number of stents and the total stent length per patient, were significantly higher in Brazillian compared to Japanese population. The use of intracoronary imaging for stent optimisation was significantly more frequent in ASET Japan than in ASET Brazil (99.6% vs. 56.0%, $p <$ 0.001).

In the ASET Japan study, pre-PCI μQFR was analysable in 207 out of 217 vessels; 10 vessels with Thrombolysis in Myocardial Infarction (TIMI) <3 flow could not be processed (Supplemental Fig. 1 A). Post-PCI μQFRs of all 217 vessels were analysable, resulting in 207 vessels with paired pre- and post-PCI μQFR.

In the ASET Brazil study, pre-PCI μQFR was analysable in 228 out of 235 vessels; 6 vessels with TIMI <3 flow and one without fluoroscopic acquisition of the entire target vessel could not be processed. Post-PCI μQFR was analysed in 231 vessels; 2 vessels with TIMI <3 flow, one without fluoroscopic acquisition of the entire target vessel, and one without available angiographic data were excluded, resulting in 227 vessels with paired pre- and post-PCI μQFR (Supplemental Fig. 1B).

3.1. Comparison of the pre-procedural physiological assessment of CAD between the two studies

The median pre-PCI μQFR was significantly lower in ASET Japan compared to ASET Brazil (0.71; IQR 0.58–0.78 vs. 0.77; IQR 0.64–0.83; $p <$ 0.001, Mann-Whitney test, Table 2, Supplemental Fig. 2 A). As shown in Supplemental Fig. 2 BC, the frequency of vessels with a pre-PCI μQFR ≤0.80 was 89.9% (186/207) in ASET Japan and 67.5% (154/228) in ASET Brazil ($p <$ 0.001).

The peak dμQFR/ds (i.e., μQFR gradient per mm) in each target vessel was higher in ASET Japan than in ASET Brazil (median 0.045/mm; IQR 0.029–0.077 vs. 0.031/mm; IQR 0.018–0.060; $p <$ 0.001) (Table 2).

Table 1
Baseline clinical characteristics.

Baseline characteristics	Total (n = 407)	Japan (n = 206)	Brazil (n = 201)	p value
Age, years (SD)	64.3 (10.0)	69.0 (9.8)	59.5 (7.7)	<0.001
Male, % (n)	73.2 (298)	81.6 (168)	64.7 (130)	<0.001
Body mass index, kg/m^2 (SD)	26.7 (4.6)	24.6 (3.9)	28.8 (4.4)	<0.001
Medical history				
Current smoking, % (n)	17.0 (69)	17.5 (36)	16.4 (33)	0.776
Diabetes mellitus, % (n)	36.4 (148)	35.9 (74)	36.8 (74)	0.851
Insulin dependent, % (n)	7.6 (31)	7.3 (15)	8.0 (16)	0.840
Hypertension, % (n)	86.2 (351)	80.1 (165)	92.5 (186)	<0.001
Dyslipidemia, % (n)	77.6 (316)	85.4 (176)	69.7 (140)	<0.001
Previous MI, % (n)	11.1 (45)	13.1 (27)	9.0 (18)	0.246
PAD, % (n)	5.9 (24)	6.3 (13)	5.5 (11)	0.349
COPD, % (n)	3.4 (14)	4.9 (10)	2.0 (4)	0.094
Renal insufficiency *, % (n)	17.4 (71)	34.5 (71)	0 (0)	<0.001
Previous PCI, % (n)	18.7 (76)	24.8 (51)	12.4 (25)	0.001
Previous CABG, % (n)	1.7 (7)	1.9 (4)	1.5 (3)	0.514
LVEF, % (SD)	62.2 (9.2)	60.5 (10.0)	64.3 (7.7)	<0.001
Anatomical SYNTAX score (SD)	7.6 (4.6)	8.0 (4.6)	7.2 (4.5)	0.066

Values are mean (SD) or n (%).
* Renal insufficiency was defined as an estimated glomerular filtration rate of creatinine clearance <60 ml/min/1.73 m^2. CABG = coronary artery bypass graft; CAD = coronary artery disease; COPD = chronic obstructive pulmonary artery disease; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; SD = standard deviation; SYNTAX = Synergy Between PCI With Taxus and Cardiac Surgery.

Table 2
Physiological characteristics.

	Japan	Brazil	p value
Pre-PCI	(n = 207)	(n = 228)	
μQFR (IQR)	0.71 (0.58–0.78)	0.77 (0.64–0.83)	<0.001
μQFR ≤0.80, % (n)	89.9 (186)	67.5 (154)	<0.001
Peak dμQFR/ds, /mm (IQR)	0.045 (0.029–0.077)	0.031 (0.018–0.060)	<0.001
PPG index	0.68 (0.60–0.79)	0.67 (0.59–0.77)	0.539
PPG index <0.78, % (n)	72.5 (150)	76.8 (175)	0.322
Max PPG 20 mm/ΔμQFR vessel (IQR)	0.76 (0.60–0.87)	0.71 (0.59–0.82)	0.130
Length with functional disease/ Total vessel length (IQR)	0.34 (0.26–0.46)	0.33 (0.22–0.44)	0.425
Post-PCI	(n = 217)	(n = 231)	
μQFR (IQR)	0.94 (0.91–0.96)	0.95 (0.92–0.97)	0.004
μQFR <0.91, % (n)	22.1 (48)	12.9 (30)	0.013
Relative μQFR gain, % (IQR) *	30.7 (21.1–54.8)	24.4 (13.8–43.1)	<0.001
Post-PCI <0.91	(n = 48)	(n = 30)	
Pre-procedural diffuse pattern, % (n) #	83.3 (40)	86.7 (26)	
Residual ***diffuse*** pressure drop post-procedure, % (n) †	85.4 (41)	90.0 (27)	
Residual major gradient, % (n)	2.1 (1)	6.7 (2)	
Site of residual peak dμQFR/ds, % (n)			
Proximal to the stented segment	39.6 (19)	40.0 (12)	
Stented segment	2.1 (1)	6.7 (2)	
Distal to the stented segment	58.3 (28)	53.3 (16)	

Values are median (IQR) or % (n).
* A relative μQFR gain was calculated in 207 and 227 vessels with paired pre- and post-PCI μQFR in the ASET Japan and the ASET Brazil study, respectively.
# Pre-procedural diffuse pattern was defined as pre-PCI PPG index <0.78.
† Residual diffuse pressure drop was defined as post-PCI PPG index <0.78. dμQFR/ds = μQFR gradient per mm; IQR = interquartile range; PCI = percutaneous coronary intervention; PPG = pullback pressure gradient; μQFR = Murray law-based quantitative flow ratio.

The median PPG index was comparable between the two groups (Japan 0.68; IQR 0.60–0.79 vs. Brazil 0.67; IQR 0.59–0.77; $p = 0.539$, Mann-Whitney test)(Table 2). In calculating the PPG index to assess the physiological distribution of CAD, the parameters of i) $\frac{Max\ PPG\ 20mm}{\Delta\mu QFR\ vessel}$ and ii) $\frac{Length\ with\ functional\ disease\ (mm)}{Total\ vessel\ length\ (mm)}$ contribute to focality and diffuseness, respectively. The median $\frac{Max\ PPG\ 20mm}{\Delta\mu QFR\ vessel}$ (0.76; IQR 0.60–0.87 vs. 0.71; IQR 0.59–0.82; $p = 0.130$, Mann-Whitney test) and the median $\frac{Length\ with\ functional\ disease\ (mm)}{Total\ vessel\ length\ (mm)}$ (0.34; IQR 0.26–0.46 vs. 0.33; IQR 0.22–0.44; $p = 0.425$) were also comparable between the two groups. Therefore, as shown in Fig. 1, the distribution of the focality and diffuseness of CAD, defined by the PPG index formula, was similar between Japanese and Brazilian populations.

3.2. Association between pre-procedural physiological patterns and haemodynamic outcomes post-procedural in the two studies

Compared to ASET Brazil, patients in ASET Japan had a significantly higher median relative μQFR gain from PCI (30.7%; IQR: 21.1–54.8 vs. 24.4%; IQR 13.8–43.1; $p < 0.001$), whereas the median post-PCI μQFR was statistically lower in the ASET JAPAN study compared to the ASET BRAZIL study (0.94; IQR 0.91–0.96 vs. 0.95; IQR 0.92–0.97; $p = 0.004$) (Table 2). The frequency of vessels with post-PCI μQFR <0.91 was 22.1% (48/217) and 12.9% (30/231) in the ASET Japan and Brazil studies, respectively ($p = 0.013$) (Table 2, Supplemental Fig. 2 BC).

A pre-procedural diffuse pattern of CAD (PPG index <0.78) with a pre-PCI μQFR <0.80 (lower left compartment in Supplemental Fig. 3AB) accounted for 79.2% (38/48) and 83.3% (25/30) of vessels resulting in a post-PCI μQFR <0.91 in ASET Japan and ASET Brazil, respectively.

In multivariable analysis of the pooled population, low pre-PCI μQFR (per 0.1 decrease; odds ratio [OR] 1.53, 95% confidence interval [CI] 1.13–2.10, $p = 0.008$) and low pre-PCI PPG index (per 0.1 decrease; OR 1.85, 95% CI 1.39–2.50, $p < 0.001$) were independent risk factors for predicting a post-PCI μQFR <0.91, whereas the use of intracoronary imaging for stent optimisation was not (OR 1.12, 95% CI 0.35–3.17, $p = 0.833$)(Supplemental Table 2). Although there were significant differences in achieving post-PCI μQFR ≥0.91 between the two studies in univariate analyses, it was no longer significant after adjustment by pre-PCI μQFR and pre-PCI PPG index (OR 1.46, 95% CI 0.52–4.68, $p = 0.497$). In both studies, the pre-PCI PPG index was an independent risk factor for predicting a post-PCI μQFR <0.91 (per 0.1 decrease of PPG index, ASET Japan: OR 1.64, 95% CI 1.14–2.42, p = 0.008; ASET Brazil: OR 2.27, 95% CI 1.43–3.71, p < 0.001) (Table 3, Fig. 2).

3.3. Distribution of residual pressure drop in the ASET Japan and ASET Brazil studies

Among vessels with post-PCI μQFR <0.91, a consistent diffuse pattern of CAD pre- and post-PCI was seen in 78.3% (36/46) and 76.7% (23/30) of vessels in ASET Japan and Brazil, respectively (lower left compartment in Fig. 3 AB); only 6.3% (3/48) and 10.0% (3/30) of vessels in the respective studies had a residual major gradient (μQFR/ds ≥0.025/mm).

Among vessels with post-PCI μQFR <0.91, residual peak dμQFR/ds was located proximal to the stented segment in 39.6% (19/48) and 40.0% (12/30), distal to the segment in 58.3% (28/48) and 53.3% (16/30), and in stented segment in only 2.1% (1/48) and 6.7% (2/30) of vessels in ASET Japan and Brazil, respectively (Fig. 3 CD, Table 2).

Table 3
Association between pre-procedural physiological characteristics and post-PCI μQFR <0.91 in the ASET Japan and ASET Brazil studies.

	Risk for post-PCI μQFR <0.91							
	ASET Japan				ASET Brazil			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Pre-PCI μQFR, per 0.1 decrease	1.31 (1.07–1.61)	0.006†	1.46 (0.97–2.22)	0.070	1.53 (1.23–1.92)	<0.001†	1.51 (0.95–2.51)	0.092
Pre-PCI PPG index, per 0.1 decrease	1.50 (1.16–1.97)	0.001†	1.64 (1.14–2.42)	0.008†	2.14 (1.53–3.11)	<0.001†	2.27 (1.43–3.71)	<0.001†
Pre-PCI dμQFR/ds, per 0.01/mm increase	1.02 (0.95–1.09)	0.531	0.99 (0.83–1.17)	0.957	1.06 (0.96–1.16)	0.189	1.05 (0.82–1.31)	0.663

Adjusted covariates included pre-procedural μQFR, μQFR-PPG index, and dμQFR/ds. CI = confidence interval; dμQFR/ds = μQFR gradient per mm; OR = odds ratio; PCI = percutaneous coronary intervention; PPG = pullback pressure gradient; μQFR = Murray law-based quantitative flow ratio.

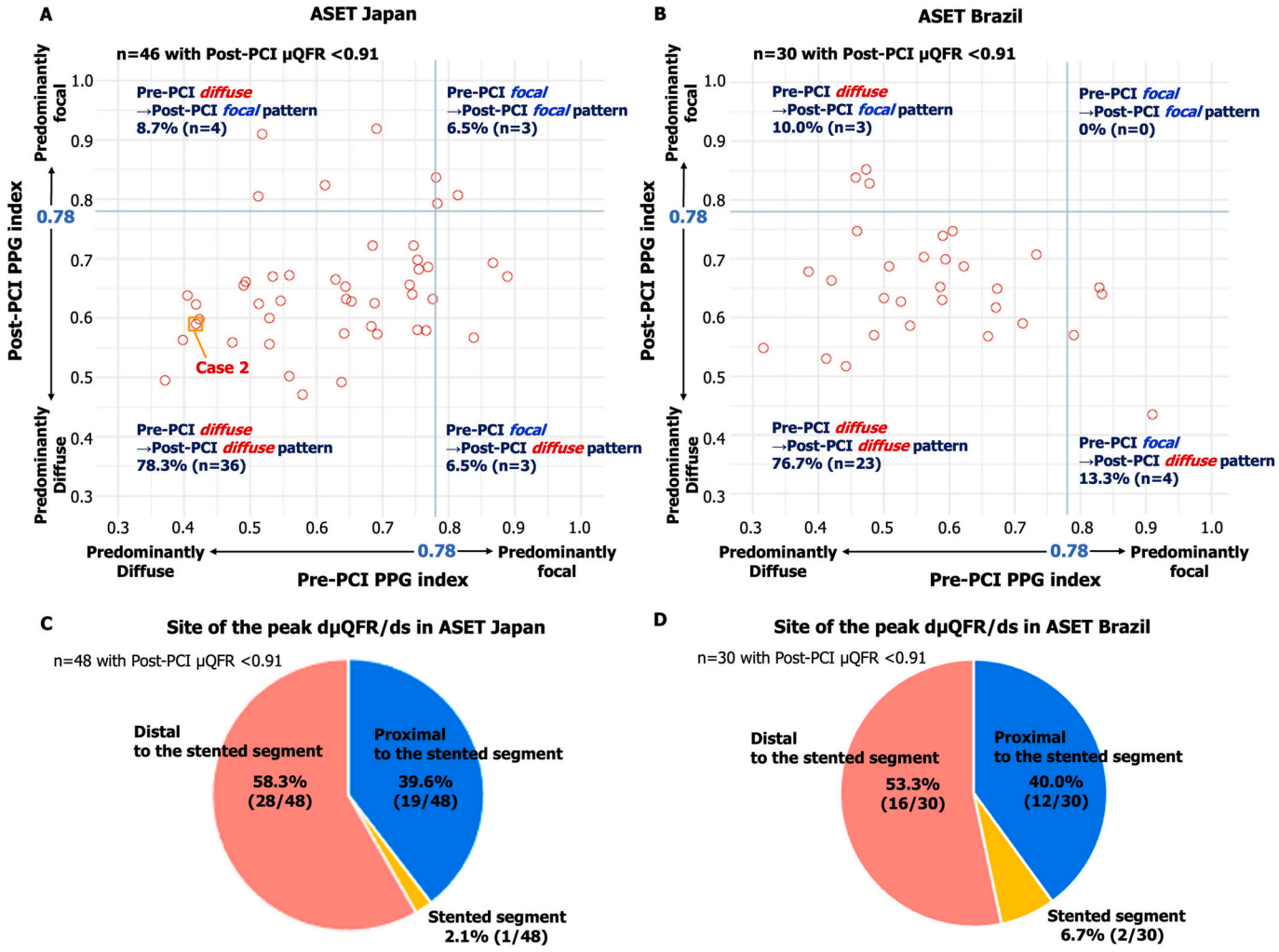

Fig. 3. The distribution of pre- and post-PCI PPG index (A, B) and sites of the residual peak dμQFR/ds (C, D) among vessels with post-PCI μQFR <0.91 in the ASET Japan and ASET Brazil studies.
Among vessels with a post-PCI μQFR <0.91, a consistent diffuse pattern of CAD pre- and post-PCI was seen in 78.3% (36/46) and 76.7% (23/30) of vessels (lower left compartment) in ASET Japan (A) and ASET Brazil (B), respectively. Case 2 with a diffuse pattern is shown in Fig. 2. Among vessels with post-PCI μQFR <0.91, residual peak dμQFR/ds was located in only 2.1% (1/48) and 6.7% (2/30) of vessels in ASET Japan (C) and Brazil (D), respectively. dμQFR/ds = μQFR gradient per mm; PCI = percutaneous coronary intervention; PPG = pullback pressure gradient.

3.4. Association between clinical baseline characteristics and physiological diffuse disease in the ASET Japan and ASET Brazil studies

The association between clinical baseline characteristics and a pre-procedural physiological diffuse pattern of CAD in the ASET Japan and ASET Brazil studies are shown in Table 4. In the multivariable analysis, diabetes mellitus was an independent risk factor for diffuse disease in ASET Japan (OR 3.10, 95% CI 1.45–7.13, $p = 0.005$), whereas age (per 1-year increase: OR 1.09, 95% CI 1.04–1.14, $p < 0.001$) and sex (male: OR 2.68, 95% CI 1.25–6.17, $p = 0.015$) were independent risk

Table 4
Association between clinical baseline characteristics and physiological diffuse disease in the ASET Japan and ASET Brazil studies.

	Risk for physiological diffuse disease (pre-PCI PPG index <0.78)							
	ASET Japan				ASET Brazil			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Age, per 1y increase	1.02 (0.99–1.06)	0.132	1.01 (0.98–1.05)	0.497	1.09 (1.04–1.14)	<0.001†	1.09 (1.04–1.14)	<0.001†
Male	1.22 (0.56–2.92)	0.630	1.14 (0.48–2.90)	0.779	2.50 (1.26–5.28)	0.011†	2.68 (1.25–6.17)	0.015†
BMI, per 1 kg/m^2 increase	1.01 (0.94–1.10)	0.735	1.00 (0.92–1.10)	0.950	0.99 (0.93–1.07)	0.840	1.00 (0.93–1.09)	0.968
Current smoking	0.79 (0.37–1.74)	0.538	0.80 (0.35–1.88)	0.606	0.72 (0.33–1.67)	0.419	0.96 (0.40–2.45)	0.932
Diabetes mellitus	3.69 (1.80–8.24)	<0.001†	3.10 (1.45–7.13)	0.005†	1.51 (0.79–2.97)	0.225	1.14 (0.53–2.49)	0.739
Hypertension	1.70 (0.81–3.49)	0.150	1.30 (0.58–2.84)	0.513	2.11 (0.69–5.98)	0.169	2.13 (0.62–6.92)	0.210
Dyslipidemia	1.84 (0.81–4.05)	0.135	1.38 (0.58–3.19)	0.450	0.74 (0.36–1.45)	0.397	0.63 (0.29–1.32)	0.233
PAD	1.20 (0.46–4.04)	0.731	1.28 (0.43–4.64)	0.677	2.05 (0.54–13.4)	0.356	1.34 (0.31–9.37)	0.727
COPD	0.65 (0.19–2.56)	0.503	0.69 (0.18–2.89)	0.586	0.60 (0.11–4.39)	0.557	0.18 (0.03–1.50)	0.078
Renal insufficiency *	3.28 (0.89–21.2)	0.121	1.95 (0.48–13.2)	0.406	–	–	–	–

Adjusted covariates included age, sex, BMI, current smoking, diabetes mellitus, hypertension, dyslipidemia, PAD, COPD, and renal insufficiency. Since no patients had renal insufficiency, it was not included in the adjusted covariates for the analysis of the ASET Brazil. * Renal insufficiency was defined as an estimated glomerular filtration rate of creatinine clearance <60 ml/min/1.73 m^2. BMI = body mass index; CI = confidence interval; OR = odds ratio; COPD = chronic obstructive pulmonary artery disease; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; PPG = pullback pressure gradient.

factors in ASET Brazil.

4. Discussion

4.1. Comparison of pre-procedural pathophysiological characteristics and their association with haemodynamic outcomes post-procedure between the two studies

Pre-PCI μQFR was significantly lower in ASET Japan than in ASET Brazil (0.71; IQR 0.58–0.78 vs. 0.77; IQR 0.64–0.83; p < 0.001). The physiological distribution of coronary atherosclerosis characterising "focality and diffuseness" was similar between the two studies (median PPG index 0.68 vs. 0.67 in ASET Japan and ASET Brazil, respectively).

Collet et al. reported that the mean PPG index derived from *invasive* pressure pullbacks during continuous hyperemia was 0.57 (SD: 0.18) [9]. Shin et al. reported that the median PPG index derived from *angiography*-based FFR was 0.78 (IQR: 0.71–0.85) in a multicenter study in the Far East [12](Fig. 1). They also observed that predominantly diffuse disease (QFR-derived PPG index <0.78) was an independent predictor of sub-optimal physiological results post-PCI, and that the rate of target vessel failure after PCI was significantly higher in patients with predominantly diffuse, as opposed to predominant focal disease. Indeed, in both the ASET Japan and Brazil studies, more than 80% of vessels with a suboptimal post-PCI μQFR had a physiological diffuse pattern of CAD pre-PCI. Our findings show that, as a continuous metric, a low μQFR-derived PPG index was an independent factor for predicting suboptimal haemodynamic outcomes immediately after PCI, which was consistent in both studies.

4.2. Combined pre-procedural physiological assessment of vessel μQFR and diffuseness of CAD

When the population was further stratified by pre-PCI μQFR (≤0.80 vs. >0.80) and pre-PCI PPG index (<0.78 vs. ≥0.78), the proportion of the vessels with predominantly diffuse disease (PPG index <0.78) without a significant pre-PCI μQFR (>0.80) — which can be interpreted as vessels having a diffuse disease with μQFR drop ≥0.0015/mm, but without a significant cumulative pressure drop along the whole target vessel — was more frequent in ASET Brazil (25.9%) than ASET Japan (7.2%) (Supplemental Fig. 3AB). It is unknown whether revascularisation could be safely deferred in these vessels; nevertheless, they would benefit from aggressive preventative therapy. In both studies, enrolment was based on investigators' discretion, although inclusion criteria required evidence of myocardial ischemia (positive non-invasive testing showing ischemia) and/or symptoms. Whilst a μQFR >0.80 in a target vessel would suggest the absence of ischaemia, and therefore PCI might be questionable, it remains plausible that diffuse CAD might actually cause symptoms. Even in the ASET Japan study, the presence of myocardial ischemia was assessed by wire-FFR, non-hyperemic pressure ratio (NHPR), or FFR_{CT} in only 25.2% (52), 18.4% (38), and 19.4% (40) of patients, respectively. Considering the feasibility of pre-PCI μQFR computation in the present study, angiography-based FFR may serve as a tool to facilitate the implementation of physiological assessment in clinical practice. In addition, Warisawa et al. reported that the physiological predominantly diffuse CAD pattern was significantly associated with discordance between FFR and instantaneous wave-free ratio (iFR) [28]. This finding suggested that in physiological diffuse disease, frictional losses along the length of the vessel would be the primary mode of pressure energy loss, evident at rest (iFR+) with only a minimal increase during hyperemia (FFR-) [28]. While the present study identified an association between a diffuse pattern and immediate hemodynamic outcomes post-PCI, further clinical studies incorporating both pre-procedural pathophysiological CAD patterns and pre-PCI FFR/iFR/angiography-based FFR are warranted to evaluate its impact on long-term clinical outcomes and to determine the best strategies.

Conversely, ASET Japan included more vessels with predominantly focal disease (PPG index ≥0.78) and a significant pre-PCI μQFR (≤0.80) than ASET Brazil (Supplemental Fig. 3AB). These vessels could be expected to benefit from stenting. In addition, it has been reported that the steep gradient of pressure drop, which is considered a physiological local severity of coronary atherosclerosis, could be a predictor of FFR gain reflecting the degree of physiological benefit from PCI [12,29]. The physiological local severity of CAD defined by peak dμQFR/ds was higher in ASET Japan than ASET Brazil (0.045/mm, IQR 0.029–0.077 vs. 0.031/mm, IQR 0.018–0.060; $p < 0.001$), resulting in the significantly higher relative μQFR gain from PCI (ASET Japan: 30.7%, IQR 21.1–54.8 vs. ASET Brazil: 24.4%, IQR 13.8–43.1, p < 0.001). On the contrary, there was no significant difference between the two populations in pre-procedural percent diameter stenosis by QCA analysis, which is a conventional, but rather non-specific parameter of the anatomical local severity of coronary atherosclerosis.

4.3. Comparison of the site of residual pressure drop post-procedure between two studies

In vessels with post-PCI μQFR <0.91, over 90% of vessels in both two studies had the residual peak dμQFR/ds in non-stented segments, with distal to the stented segment most common. Conventional strategies to optimise the overall haemodynamic outcome include post-dilatation of the stent, or if this proves ineffective, additional stenting or use of a drug

coated balloon in non-stented segments. However, over 85% of vessels in the two studies with a suboptimal post-PCI μQFR (<0.91) had a residual *diffuse* pressure drop post-PCI according to the PPG index (<0.78), and less than 10% had a residual major gradient (μQFR/ds ≥0.025/mm). Hence these vessels are unlikely to benefit from additional stenting due to the widespread and steady residual pressure drop without any steep identifiable gradient.

4.4. Predictive risk for sub-optimal haemodynamic outcomes immediately post-procedure

The median post-PCI μQFR was statistically lower in ASET Japan than in ASET Brazil. However, in the multivariable analysis of the pooled population of both studies, when pre-PCI μQFR and pre-PCI PPG index were included as adjusted covariates, the study population had no impact on the risk of sub-optimal haemodynamic outcomes. This suggests that the lower pre-PCI μQFR in the ASET Japan population impacted the difference in post-PCI μQFR between the two populations. The use of intracoronary imaging for stent optimisation was not directly associated with a reduction in the risk of suboptimal haemodynamic outcomes. A possible explanation for this is that residual lesions were disseminated along the entire vessel, and not localised to a focal point that could be easily detected by intracoronary imaging and receive additional percutaneous treatment. Of note, both populations had a relatively high prevalence of a diffuse pattern of CAD, with lower median values of pre-procedural angiography-derived PPG index when compared to previous reports [12,14].

4.5. Predictive risk factors of physiological diffuse disease and its geographic disparity

There was a geographic disparity in the clinical risk factors associated with physiological diffuse disease in the two study populations. In the ASET Japan population, the independent risk factor was diabetes mellitus, which is modifiable, while in ASET Brazil it was age and sex. Given that the physiological diffuse pattern of CAD was associated with sub-optimal results post-PCI, attention should be focused on controlling these modifiable risk factors of the development and progression of diffuse disease. Furthermore, predictive biomarkers for diffuse disease warrant investigation in future studies to detect optimal targets for prevention using powerful antiatherogenic therapy such as micro-RNA inhibiting PCSK-9, lipoprotein (a), high-sensitivity C-reactive protein, and IL-6 [30], whilst considering geographic disparities.

4.6. Study limitations

Angiography-derived FFR was analysed retrospectively, and the results of this proof-of-concept study are only hypothesis-generating. This is a specific population of CCS, and the findings are not applicable to acute coronary syndrome or other indications. Invasive FFR as the gold standard of physiological assessment for intermediate coronary stenosis was not performed, although excellent correlation of $r = 0.90$ ($p < 0.001$) and agreement (mean difference: 0.00 [SD: 0.05], $p = 0.378$; intraclass correlation coefficient for the absolute value = 0.91 [95% CI: 0.89–0.92]) with wire-based FFR have been shown [20].

5. Conclusions

There was a geographic disparity in preprocedural angiography-based pathophysiological characteristics. The combined pre-procedural physiological assessment of vessel μQFR and diffuseness/focality of CAD potentially identifies patients who will benefit most from PCI.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2024.131805.

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