BMC Gastroenterology

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The impact of relaxing the requirements for dyspeptic Symptom Onset frequency or duration in Rome IV Criteria on the Symptom Pattern and diagnosis of functional dyspepsia

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Abstract

Background The Rome IV criteria for functional dyspepsia (FD) has strict requirements for symptom frequency and onset duration, making it difficult for patients to meet these criteria in clinical practice. This study aimed to investigate the impact of relaxing the Rome IV criteria on the diagnosis and symptom pattern of FD.

Methods A cross-sectional, multi-center study was conducted involving 2935 consecutive broadly defined FD patients without positive findings on upper gastrointestinal endoscopy or routine examinations. Questionnaires were used to collect demographic and upper gastrointestinal symptom data. Symptom pattern was compared between Rome IV criteria defined FD patients and those defined by relaxed Rome IV criteria.

Results Only 22.2% of broadly defined FD patients rigorously fulfilled Rome IV criteria. No significant difference was found for proportion of patients with dyspeptic symptoms, dysmotility-like symptoms, reflux-like symptoms, as well as severity and onset frequency of dyspeptic symptoms (all $P > 0.05$), between patients who didn't fulfill Rome IV criteria for FD solely due to a duration of 3–6 months and Rome IV criteria defined FD patients. Patients with broadly defined postprandial distress syndrome (PDS) who didn't fulfill Rome IV criteria solely due to a symptom frequency of 1–2 days per week had significantly lower symptom severity ($P < 0.001$), but similar postprandial symptom characteristics compared to those defined by the Rome IV criteria.

Conclusions A symptom duration criterion of 3 months may be sufficient for diagnosing FD. Reducing the symptom onset frequency to no less than 1 day per week in the Rome IV criteria for PDS does not affect its postprandial symptom characteristics.

Keywords Functional dyspepsia, Rome IV criteria, Epigastric pain syndrome, Postprandial distress syndrome

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Introduction

Functional dyspepsia (FD) is one of the most common functional gastrointestinal disorders, affecting approximately 7.2% of the general population worldwide [1]. FD is defined as "the presence of symptoms thought to originate from the gastroduodenal region, in the absence of organic disease that is likely to explain the symptoms" [2]. Characteristic symptoms for FD include epigastric pain, epigastric burning, postprandial fullness, or early satiety, fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis according to Rome IV criteria [3]. As a chronic functional disorder of the gastrointestinal tract with no explanation for their symptoms at endoscopy and usual examinations, FD affects quality of life and social function, imposing a heavy social and economic burden [4–6].

FD is considered a heterogeneous condition with different underlying pathophysiological mechanisms, which may negatively impact the efficacy of therapeutic interventions targeting a single mechanism [2]. Rome IV criteria subdivided FD into postprandial distress syndrome (PDS), which is characterized by meal-related symptoms such as early satiation and fullness, and epigastric pain syndrome (EPS), which refers to epigastric pain or epigastric burning that does not occur exclusively postprandially, can occur during fasting, and can be even improved by meal ingestion [3]. Symptoms associated with PDS were generally thought to originate from gastric motor dysfunction, while those associated with EPS were commonly accepted to be due to mechanical hypersensitivity of the stomach [5]. However, using the type of symptoms in FD to guide treatment choice was not recommended by the ACG and CAG Clinical Guideline for no strong clinical evidence exiting [7].

The Rome IV criteria require FD diagnosis to fulfill the symptom duration criteria for at least 3 months, with symptom onset at least 6 months before diagnosis [3]. However, a Japanese survey showed that dyspeptic patients generally visited a medical facility within a month of symptom onset, resulting in them not meeting the Rome IV criteria for symptom duration [8]. Furthermore, the Rome IV criteria for PDS, which require symptoms to occur at least 3 times a week after ordinary-sized meals, may be too strict for diagnosing PDS in routine clinical practice [9]. Unfortunately, limited research has been conducted on this topic to date.

In this study, we enrolled dyspepsia patients with no positive findings from 100 hospitals in China as the primary research subjects. The aim of this study was to (i) describe the symptom characteristics of Rome IV criteria defined FD in China and explore the heterogeneity of symptom pattern among sub-types for FD; (ii) explore the impact of relaxing the requirements for symptom onset frequency, severity, and duration of the Rome IV criteria on diagnosing FD.

Methods

We conducted a multicenter, cross-sectional study of consecutive outpatients from 100 Chinese hospitals in nine provinces or cities including Beijing, Shanghai, Guangdong, Jiangsu, Shandong, Zhejiang, Heilongjiang, Hunan, and Hubei province between May 2016 and January 2018. Consecutive dyspeptic patients without positive findings by upper gastrointestinal endoscopy or routine blood examinations were asked to fill out a questionnaire with supplementary questions via WeChat application which were explained in advance by trained researchers. Ethics Committee of Union Hospital of Tongji Medical College Huazhong University of Science and Technology approved this study. Oral informed consent was obtained from all the included patients. All authors had access to the study data and approved the final manuscript.

Inclusion criteria

Inclusion criteria were (i) aged 18 years and older; (ii) dyspeptic symptoms were present (at least with 1 or more symptoms that included postprandial fullness, early satiation, epigastric pain and epigastric burning); (iii) patients visited the gastroenterology clinics and completed upper gastrointestinal endoscopy at the same visit during the study period. *H Pylori* infection status was neither an inclusion nor exclusion criterion.

Exclusion criteria

Exclusion criteria were (i) positive findings by upper gastrointestinal endoscope which can explain dyspeptic symptoms, such as esophagitis, gastric ulcer, duodenal ulcer and chronic atrophic gastritis; (ii) patients who were pregnant or lactating; (iii) history of major abdominal surgery; (iv) severe neuropsychiatric disease or severe liver, kidney, or respiratory disease; (v) pancreaticobiliary disease or metabolic disease (thyroid dysfunction and diabetes), liver dysfunction; (vi) current use of steroids or nonsteroidal anti-inflammatory drugs; (vii) patients who declined to participate in this study.

Data collection

The basic demographic data collected included name, age, height, weight, sex, nature of work and working tension. The symptom data included gastrointestinal symptoms, symptom onset duration, symptom frequency per week, symptom severity and relation between eating and symptom. A trained researcher imported all the related data into the database. The severity of the symptoms was graded 0–3 according to symptom impact on patients' daily activities; 0: absent, 1: mild, 2: moderate

(not interfering with daily activities), 3: severe (interfering with daily activities).

Definitions of broadly defined FD and Rome IV criteria defined FD

Broadly defined FD was defined as the presence of any epigastric pain, epigastric burning, postprandial fullness, or early satiety with no evidence of abnormal upper gastrointestinal endoscopy that were likely to explain the symptoms, regardless of symptom frequency, severity or onset duration. The Rome IV criteria defined FD was strictly diagnosed according to the Rome IV criteria with symptom severity at least being moderate.

Table 1 Demographic data and baseline characteristics of all participants

	Potential FD	Rome IV criteria defined FD	Broadly defined FD
N	**2284**	**651**	**2935**
Gender (N%)			
Male	54.9	70.2	58.3
Female	45.1	29.8	41.7
Age (N%, year)			
Mean (SD)	43.3 (11.05)	44.4 (11.00)	43.5 (11.05)
18–35	25.4	21.4	24.5
36–59	62.7	67.6	63.8
> 60	11.9	11.1	11.7
BMI (N%, kg/m^2)			
Mean (SD)	23.4 (3.86)	23.7 (3.84)	23.5 (3.86)
< 18.5	9.7	8.4	9.4
18.5–23.9	48.2	45.3	47.5
> 24	42.2	46.2	43.1
Education level (N%)			
Elementary or below	18.1	30.0	20.7
High school	26.8	26.6	26.7
College or above	55.1	43.5	52.5
Job category (N%)			
Physical	19.2	34.1	22.5
Mental	39.0	30.4	37.1
Middle	31.7	23.2	29.8
Unemployed	10.1	12.3	10.6
Working tension (N%)			
Not nervous	21.4	35.3	24.5
Normal	32.7	27.6	31.6
Nervous	37.5	28.7	35.5
Very nervous	8.4	8.3	8.4

BMI, body mass index; **FD**, Functional Dyspepsia

Values are expressed as the mean (standard deviation) or N%

Broadly defined FD, defined as the presence of any epigastric pain, epigastric burning, postprandial fullness, or early satiety with no evidence of abnormal upper gastrointestinal endoscopy that were likely to explain the symptoms, regardless of symptom frequency, severity, or onset duration

Potential FD, defined as broadly defined FD but not fulfilled Rome IV criteria

Subgroup classification for FD

The Rome IV criteria subdivide FD patients into Postprandial Distress Syndrome (PDS) and Epigastric Pain Syndrome (EPS). Then, the overlapping EPS-PDS subgroup (overlap-FD) was comprised of patients with both PDS and EPS symptoms. Finally, patients in overlap-FD group with postprandial epigastric pain and postprandial nausea were considered as PDS (Details in [3]). Subgroup classification for broadly defined FD was the same as above, however, regardless of symptom frequency, severity, or onset duration.

Statistical analysis

EpiData 3.1 software was used for data collection. SPSS 20.0 was used for statistical analysis. The presence and severity of symptoms was defined and proportions of patients with symptoms were compared using Pearson's chi-square test or the Fisher exact test was used according to the analysis requirements. The results of continuous variables were expressed as the mean (standard deviation), and the independent-samples T test or one-way analysis of variance (ANOVA) test was used according to the analysis requirements. Bonferroni corrections were applied to correct for multiple tests. P values < 0.05 were considered statistically significant.

Results

Patient characteristics

A total of 2935 patients (41.7% females, 43.5 ± 11.05 years old and BMI of 23.48 ± 3.86 kg/m^2) diagnosed as broadly defined FD patients were enrolled in the study. Of these, only 22.2% (651/2935) patients strictly met the Rome IV criteria for FD. We defined those broadly defined FD patients who didn't meet the Rome IV criteria for any reason as potential FD patients. For potential FD patients, 20.3% were classified as EPS alone, 41.4% as PDS alone and 38.2% as overlap-FD. For the Rome IV criteria defined FD, the percentages were 50.3%, 28.7% and 17.5%, respectively (Tables 1**and** Fig. 1).

Reasons for why potential FD patients did not meet Rome IV criteria

For those broadly defined FD patients that not meeting the diagnostic criteria, 75.8% (1731/2284) of them reported their symptoms were not severe enough to impact on usual activities. Moreover, the symptom onset duration for 39.2% (894/2284) of them was less than 6 months. 5.6%, 77.9% and 77.7% of those broadly defined EPS, PDS and overlap-FD, respectively, were with lower symptom onset frequency than the requirements in the Rome IV criteria. (Table 2).

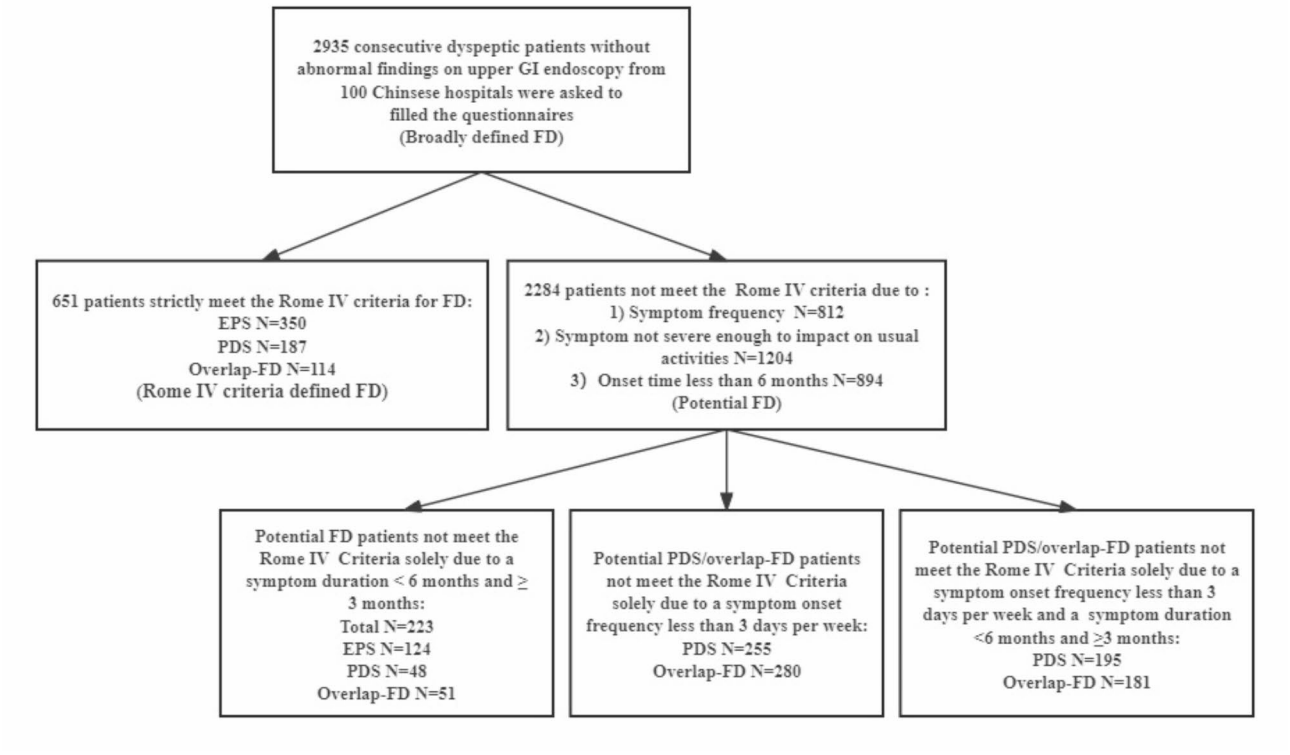

Fig. 1 Flow diagram of this study. **FD**, Functional Dyspepsia; **EPS**, epigastric pain syndrome; **PDS**, Postprandial fullness syndrome; **Overlap-FD**, EPS-PDS overlapping FD. **Broadly defined FD**, defined as the presence of any epigastric pain, epigastric burning, postprandial fullness, or early satiety with no evidence of abnormal upper gastrointestinal endoscopy that were likely to explain the symptoms, regardless of symptom frequency, severity, or onset duration. **Potential FD**, defined as broadly defined FD but not fulfilled Rome IV criteria

Symptom pattern of Rome IV criteria-defined FD

Of all patients involved in this study, 651 fulfilled Rome IV criteria for FD rigorously (29.8% females, 44.4±11.00 years old and BMI of 23.7±3.84 kg.m^2). 48.5% and 26.3% of them experienced dysmotility-like symptoms (any belching, nausea, or vomiting) and reflux-like symptoms (any heartburn, acid flux or Non-acid reflux), respectively. More than 60% of them reported their dyspeptic symptoms to be aggravated by the meal. Dyspeptic symptoms profoundly affected daily life in 23.8% of them. The mean frequency of symptom episodes 3.4±1.79 times per week (Table 3).

For three sub-types of these FD patients, dysmotility-like symptoms occurred more frequently in PDS and overlap FD than EPS (both $P<0.05$). Compared with PDS, significantly higher proportion of EPS and overlap FD had any reflux-like symptoms (19.81% vs. 5.88%, $P<0.05$) (Table 3).

For patients of different genders, we observed that female FD patients were more likely to experience dysmotility-like symptoms (68.0% vs. 40.3%, $P<0.001$) such as belching and nausea, while male FD patients suffered from reflux-like symptoms more frequently (32.6% vs. 11.3%, $P<0.001$) **(Supplementary Table 1)**.

For sub-group analysis based on age, significantly higher proportion of elder patients (aged > 60 years) experienced dysmotility-like symptoms than younger patients (aged < 35 years) (62.5% vs. 25.2%, $P<0.001$), while as for reflux-like symptoms, the proportion of elder patients was significantly lower (8.3% vs. 18.0%, $P<0.001$). Moreover, near half of younger patients reported to suffer from severe dyspeptic symptoms, the percentage of which was higher than elder patients' (46.8% vs. 26.4%, $P<0.001$) **(Supplementary Table 2)**.

Comparison of symptom pattern between Rome IV criteria defined FD and FD with short disease duration.

FD with short disease duration in the present study was defined as dyspeptic patients who meet the Rome IV criteria but with a dyspeptic duration ≥ 3 months and ≤ 6 months. A total of 233 patients met this criterion. For upper gastrointestinal symptoms mentioned in this study, there was almost no difference between the two groups except epigastric burning (41.6% vs. 51.1%, $P=0.014$). In most patients of both groups, their global symptom would be worsened after a meal (60.4% vs. 64.1%, $P=0.474$). In the analysis of subgroups based on sub-type of FD (Table 3), age **(Supplementary Table 2)**, gender **(Supplementary Table 1)**, the symptom patterns of both groups were also found to be similar.

Table 2 Dyspepsia symptoms characteristics of all broadly defined FD

	Potential FD				Rome IV criteria defined FD				Broadly defined FD
	EPS	PDS	Overlap	Total	EPS	PDS	Overlap	Total	
N	**464**	**946**	**874**	**2284**	**350**	**187**	**114**	**651**	**2935**
Dyspepsia symptom severity (N%)									
Mild	62.1	54.4	45.9	52.7	0	0	0	0	41.0
Moderate	30.0	39.5	46.6	40.3	77.4	69.0	84.2	76.2	48.2
Severe	8.0	6.0	7.6	7.0	22.6	31.0	15.8	23.8	10.7
Dyspepsia symptom frequency (N%, days per week)									
< 1	5.6	0.4	3.5	2.7	0	0	0	0	2.1
`1	24.8	29.0	33.0	29.6	38.9	0	0	20.9	27.7
2	35.8	48.5	41.1	43.1	24.3	0	0	13.1	36.4
3	1.9	2.9	2.6	2.6	2.6	19.8	15.8	9.8	4.2
4	21.8	10.6	9.5	12.4	22.9	48.1	44.7	33.9	17.2
5	5.8	4.0	4.8	4.7	8.9	11.8	21.1	11.8	6.3
6	0.4	0.6	0.3	0.5	0.3	1.1	3.5	1.1	0.6
7	3.9	4.0	5.1	4.4	2.3	19.3	14.9	9.4	5.5
Dyspepsia symptom onset duration (N%)									
< 3 months	9.5	4.9	4.8	5.8	0	0	0	0	4.5
3–6 months	44.4	29.7	31.5	33.4	0	0	0	0	26.0
6–12 months	24.1	36.8	35.9	33.9	65.1	51.3	57.0	59.8	39.6
> 12 months	22	28.6	27.8	27	34.8	48.6	43.0	40.2	29.9

Values are expressed as N%

FD, Functional Dyspepsia; **EPS**, epigastric pain syndrome; **PDS**, Postprandial fullness syndrome

Rome IV criteria defined FD was strictly diagnosed according to the Rome IV criteria with symptom severity at least being moderate

Broadly defined FD, defined as the presence of any epigastric pain, epigastric burning, postprandial fullness, or early satiety with no evidence of abnormal upper gastrointestinal endoscopy that were likely to explain the symptoms, regardless of symptom frequency, severity, or onset duration

Potential FD, defined as broadly defined FD but not fulfilled Rome IV criteria

Comparison of symptom pattern between PDS/overlap-FD with low symptom onset frequency and Rome IV criteria defined PDS/overlap-FD.

A total of 187 PDS patients and 114 overlap-FD patients who met Rome IV criteria were identified. 450 potential PDS patients and 461 potential overlap-FD patients who failed to meet the Rome IV criteria were divided into four groups according to age and frequency of onset, respectively, and then were compared with Rome IV criteria defined PDS/overlap-FD in terms of symptom characteristics.

For PDS, the incidence of epigastric burning was significantly higher in low-frequency PDS group compared with Rome IV-defined PDS group (all $P<0.05$). The proportions of dysmotility-like symptoms and reflux-like symptoms were similar between groups. The proportion of postprandial symptom aggravation was more than 80% between two groups. Patients with severe overall symptom were more common in Rome IV criteria defined PDS group (all $P<0.001$) (Table 4).

We also observed similar postprandial symptom characteristic and overall symptom severity between potential overlap-FD and Rome IV criteria defined overlap-FD (Table 5).

The impact of relaxing the requirements in Rome IV criteria for the frequency and onset duration of dyspeptic symptoms on the diagnosis of FD.

According to the Rome IV criteria, only 22.2% dyspeptic patients without positive finding in upper gastrointestinal endoscopy can be diagnosed as FD. When reducing the requirement for symptom duration in the Rome IV criteria to 3 months, 7.9% of potential FD (including 26.7% of potential EPS, 5.1% of potential PDS, and 5.8% of potential overlap-FD) would be diagnosed as FD. Moreover, when relaxing the requirement for symptom onset frequency of PDS and overlap-FD in the Rome IV criteria to 1 days per week, another 27.0% and 32.0% of them respectively would be identified. When relaxing the requirements in Rome IV criteria for the frequency and onset duration at the same time according to above, the diagnose rate for potential FD would be increased to 49.6% (1134/2284), including 27.0% (124/464) of potential EPS, 52.6% (498/946) of potential PDS, and 58.6% (512/874) of potential overlap-FD.

Discussion

In the present study, a self-administered questionnaire survey including gastrointestinal symptoms and demographic characteristics was conducted among patients

Table 3 Comparing symptom pattern between Rome IV criteria defined FD patients and potential FD patients with a 3–6 months' duration

	EPS			PDS			Overlap-FD			Total FD			Within sub-types of Rome IV criteria defined FD (duration ≥ 6 months)	
Symptom duration	**≥ 6 months**	**3–6 months**	***P***	**≥ 6 months**	**3–6 months**	***P***	**≥ 6 months**	**3–6 months**	***P***	**≥ 6 months**	**3–6 months**	***P***	***P*#**	**Post hoc$**
N	350	124		187	48		114	51		651	223			
Dyspepsia symptoms (N%)														
Epigastric pain	87.4	92.7	0.107	43.9	41.7	0.785	74.6	64.7	0.195	72.7	75.3	0.435	**< 0.001**	a, b,c
Postprandial fullness	0.0	0.0		79.1	89.6	0.098	87.7	86.3	0.797	38.1	39.0	0.808	**< 0.001**	a, b,c
Early satiation	0.0	0.0		67.9	62.5	0.477	62.3	62.7	0.955	30.4	27.8	0.461	**< 0.001**	a, b,b
Epigastric burning	56.6	62.9	0.219	12.8	14.6	0.749	43.0	56.9	0.099	41.6	51.1	**0.014**	**< 0.001**	a, b,c
Dysmotility-like symptoms (N%)														
Any	29.1	25.0	0.378	65.8	66.7	0.907	79.8	80.4	0.933	48.5	46.6	0.623	**< 0.001**	a, b,c
Belching	11.7	10.5	0.711	58.3	58.3	0.996	64.0	68.6	0.566	34.3	34.1	0.962	**< 0.001**	a, b,b
Nausea	25.1	23.4	0.697	11.2	14.6	0.522	34.2	29.4	0.544	22.7	22.9	0.967	**< 0.001**	a, b,a
Vomiting	0.0	0.0		2.7	4.2	0.634	1.8	3.9	0.588	1.1	1.8	0.406	**0.024**	a, b,b
Reflux-like symptoms (N%)														
Any	28.9	38.7	**0.042**	19.3	18.8	0.937	29.8	25.5	0.569	26.3	31.4	0.140	**< 0.001**	a, b,ab
Heartburn	11.1	8.9	0.479	2.7	2.1	0.999	9.6	11.8	0.680	8.4	8.1	0.861	**0.003**	a, b,a
Acid reflux	29.4	39.5	**0.039**	19.3	18.8	0.937	17.5	13.7	0.540	24.4	29.1	0.650	**0.006**	a, b,b
Non-acid reflux	5.4	4.0	0.542	0.0	0.0		5.3	2.0	0.438	3.8	2.7	0.423	**0.005**	a, b,a
Symptoms after meals (N%)			0.100			0.550			0.108			0.474	**< 0.001**	
Aggravation	52.6	59.7		84.5	85.4		44.7	54.9		60.4	64.1			a, b,a
Relief	27.4	17.7		8.0	4.2		26.3	31.4		21.7	17.9			a, b,a
No change	20.0	22.6		7.5	10.4		28.9	13.7		18.0	17.9			a, b,a
Dyspepsia symptom severity (N%)			0.582			0.416			0.498			0.576		
Moderate	77.4	75.0		69.0	75.0		84.2	88.2		76.2	78.0		**0.008**	ab, b,a

Table 3 (continued)

	EPS			PDS			Overlap-FD			Total FD			Within sub-types of Rome IV criteria defined FD (duration ≥ 6 months)	
Symptom duration	**≥ 6 months**	**3–6 months**	***P***	**≥ 6 months**	**3–6 months**	***P***	**≥ 6 months**	**3–6 months**	***P***	**≥ 6 months**	**3–6 months**	***P***	***P*** [#]	**Post hoc** [$]
Severe	22.6	25.0		31.0	25.0		15.8	11.8		23.8	22.0			
Dyspepsia symptom frequency Mean (SD)	2.5 (1.59)	2.7 (1.68)	0.320	4.5 (1.35)	4.4 (1.20)	0.705	4.6 (1.24)	4.5 (1.22)	0.701	3.4(1.79)	3.5(1.74)	0.869	**< 0.001**	a, b,b

EPS, epigastric pain syndrome; **PDS**, postprandial distress syndrome. **Potential FD patients with a 3–6 month duration** are those who do not meet the Rome IV criteria solely because of the onset duration

The results of categorical variables were expressed as N%, Pearson's chi-square test or the Fisher exact test was used according to the analysis requirements. The results of continuous variables were expressed as the mean (standard deviation), and the independent-samples T test or one-way analysis of variance (ANOVA) test was used according to the analysis requirements

$P < 0.05$ indicates a statistical difference between groups. [#] < 0.05 indicates a statistical difference among EPS, PDS, and overlap-FD defined by Rome IV criteria (disease duration ≥ 6 months)

[$] Post hoc analyses were using Bonferroni method. Three sets of comma-separated letters represent EPS, PDS, and overlap-FD defined by Rome IV criteria (disease duration ≥ 6 months), and if the same letter is not present in the two groups, it indicates a statistical difference between the two groups

who visited hospitals for dyspepsia symptoms but without positive findings in upper gastrointestinal endoscopy. This was a multi-center, large-sample, cross-sectional study examining differences of symptom pattern among sub-types of Rome IV criteria defined FD patients. Moreover, we also explored the influence of relaxing the requirements in Rome IV criteria for disease duration and symptom onset frequency on the diagnosis of FD. The main results of the present study showed that (i) symptoms of PDS/overlap FD were more frequently aggravated by a meal than those of EPS; (ii) shortening the symptom onset duration of Rome IV criteria for FD from 6 to 3 months did not affect its symptom pattern; (iii) potential PDS and overlap-FD with symptom onset 1–2 days per week had similar postprandial symptom characteristics with those defined by Rome IV criteria, but with lower symptom severity level.

The Rome III consensus proposed to subdivide FD patients with meal-related FD symptoms (PDS) and patients with meal-unrelated FD symptoms (EPS). PDS comprises FD patients who experience bothersome postprandial fullness and/or early satiation at least several times a week. EPS includes patients experiencing epigastric pain or burning at least once a week. However, a large overlap between PDS and EPS hampers the usefulness of the subdivision [10]. To address this gap, the Rome IV criteria considered postprandial epigastric pain or burning, epigastric bloating, excessive belching, and nausea as part of PDS symptoms [10], which significantly reduces the overlap between PDS and EPS groups [2, 10]. Meals has been confirmed to play a crucial part in the triggering or aggravation of symptoms in FD by previous studies [2, 11–14]. Furthermore, a study demonstrated that the Rome IV criteria for PDS successfully identify a patient group whose symptoms are associated with the meals, meanwhile the symptoms of Rome IV criteria defined EPS patients and of Rome IV criteria defined overlap subgroup patients lack a clear link to the meal [2]. In line with this concept, our data supported that symptoms of PDS population were more likely to be aggravated after a meal than EPS or overlap-FD based on the Rome IV criteria. Along with this, PDS were found more frequently to experience dysmotility-like symptoms (such as belching and nausea) than EPS, while EPS patients were more likely to suffer from reflux-like symptoms, such as acid reflux and heartburn. Above results suggest a different pathophysiological basis for symptom generation between EPS and PDS. Traditionally, while PDS is mainly considered a disorder of motor control, EPS has been related to gastric and duodenal (acid or mechanical distention) hypersensitivity, H. pylori infection and low-grade inflammation, and increased mucosal permeability in the duodenum [4–6, 15]. However, studies are still needed to determine if subdivision according to Rome

Table 4 Comparing symptom pattern between Rome IV criteria defined PDS and potential PDS

	Rome IV criteria defined PDS	PDS with low symptom frequency				*P*			
Group	**1**	**2**	**3**	**4**	**5**	**1 vs. 2**	**1 vs. 3**	**1 vs. 4**	**1 vs. 5**
Symptom duration	**≥ 6 months**	**≥ 6 months**	**≥ 6 months**	**3-6months**	**3-6months**				
Symptom frequency (days per week)	**3–7**	**1**	**2**	**1**	**2**				
N	187	89	166	70	125				
Dyspepsia symptom (N%)									
Epigastric pain	43.9	44.9	53.0	46.8	49.1	0.864	0.086	0.501	0.265
Postprandial fullness	79.1	93.3	83.1	88.5	86.4	**0.003**	0.340	**0.003**	**0.039**
Early satiation	67.9	57.3	80.1	72.1	77.8	0.085	**0.009**	0.302	0.018
Epigastric burning	12.8	33.7	50.6	38.7	41.9	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**
Dysmotility-like symptoms (N%)									
Any	65.8	56.2	69.3	65.2	67.7	0.123	0.484	0.890	0.658
Belching	58.3	44.9	56.0	53.2	56.3	0.038	0.668	0.246	0.666
Nausea	11.2	19.1	21.1	19.9	18.3	0.076	0.011	**0.010**	**0.039**
Vomiting	2.7	4.5	5.4	5.1	4.7	0.665	0.187	0.171	0.276
Reflux-like symptoms (N%)									
Any	19.3	25.8	13.9	16.9	13.3	0.212	0.175	0.487	0.081
Heartburn	2.7	21.3	1.8	7.6	1.8	**< 0.001**	0.727	**0.019**	0.520
Acid reflux	19.3	6.7	13.9	11.5	13.3	**0.007**	0.175	**0.012**	0.081
Non-acid reflux	0.0	0.0	0.0	0.0	0.0				
Symptoms after meals (N%)						**0.019**	0.312	0.090	0.426
Aggravation	84.5	83.1	84.9	85.5	86.4				
Relief	8.0	15.7	10.8	10.8	9.0				
No change	7.5	1.1	4.2	3.7	4.7				
Overall symptom severity (N%)						**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**
Moderate	69.0	88.8	86.1	86.0	84.9				
Severe	31.0	11.2	13.9	14.0	15.1				

PDS, postprandial distress syndrome. **Potential PDS patients** are those who do not meet the Rome IV criteria solely because of the onset duration and/or the symptom onset frequency

The results of categorical variables were expressed as N%, Pearson's chi-square test or the Fisher exact test was used according to the analysis requirements. $P<0.05$ indicates a statistical difference

IV criteria is associated differently with psychological comorbidities and treatment responses [10]. The research revealed notable variations in symptom patterns among patients with functional dyspepsia (FD), taking into account their age and gender. This discovery highlights the importance of considering individual characteristics when diagnosing and treating FD and suggests the need for personalized approaches to patient care. Further investigation into these differences may lead to improved understanding and management of this condition.

Inconsistent with one previous study from China [16], which reported that the prevalence of FD in patients who visited a hospital complaining of dyspepsia is approximately half of cases based on Rome IV criteria, in the present study, only 22% of dyspeptic patients with no evidence of abnormal upper gastrointestinal endoscopy fulfilled Rome IV criteria for FD rigorously. Perhaps because of relatively low medical costs in China (each gastroscopy usually costs less than $100), dyspeptic patients generally visit a medical facility within 6 months of symptom onset, and the proportion in the present study was more than 30%. As a result, these patients did not meet the Rome IV criteria for duration of symptoms (onset at least 6 months previously and symptoms persisting for at least 3 months), and therefore cannot be diagnosed with FD under the criteria, resulting in a lack of timely and effective clinical intervention. Two previous studies in Japan revealed similar results, which attributed to almost universal health insurance coverage [8, 17]. Thus, we further analyzed the pattern of upper gastrointestinal symptoms between Rome IV criteria defined-FD patients and those who didn't fulfilled Rome IV criteria for FD solely due to a duration of 3-6 months. However, few significant differences between two groups were found, as well as in the subgroup analyses (including BMI, gender, age, and subtype of FD). Hence, symptom duration for 3 months may be enough to diagnose a FD in clinical practice in China.

Mainly the frequency of symptoms is taken into account to establish the presence of FD according to the Rome IV criteria [18]. The PDS subgroup is defined by the presence of postprandial fullness and/or early satiation after normal-sized meals at 3 times per week. The overlapping EPS-PDS (overlap FD) subgroup was comprised of patients with both PDS and EPS symptoms according to Rome III definitions. The Rome IV classification identified PDS and EPS on similar grounds, but also considered postprandial epigastric pain and postprandial nausea as PDS symptoms. The cut-off of frequency of symptoms to diagnose PDS or overlap FD still needs to be discussed. In the present study, we defined PDS/overlap-FD with symptom onset frequency less than 3 days per week as low-frequency PDS/overlap-FD, which didn't meet the Rome IV criteria. Low-frequency PDS/overlap-FD was found to account for over 70% of each subgroup. In addition, Low-frequency PDS had almost similar incidence of dysmotility-like symptoms, reflux-like symptoms and postprandial symptom characteristic as Rome IV criteria defined PDS, though with relatively lower overall symptom severity. Above similar symptom pattern, including symptom severity, was also present between low-frequency overlap FD and Rome IV criteria defined overlap FD.

The present study had several limitations. First, it is a retrospective cross-sectional study, with no follow-up on the long-term clinical outcomes of the potential FD patients. Thus, whether potential FD and Rome IV criteria defined FD have the same pathological mechanism and clinical response remains unverified. Secondly, this is a questionnaire-based study, although we provided sufficient explanations to the participants beforehand, there is a possibility of recall bias or response bias. Furthermore, this research was solely on the upper abdominal symptoms of patients, while neglecting the symptoms related to the lower abdomen and mental health. However, the majority of FD patients have an overlapping disorder (such as gastroesophageal reflux disease, irritable bowel syndrome, constipation [19], and anxiety-depression [20–24]), that is associated with more severe symptoms and poorer treatment outcomes [19]. Although epidemiological studies show that *H pylori* infection is associated with dyspepsia in the general population, the magnitude of the association is modest [25]. Since *H Pylori* testing isn't routinely done in dyspeptic patients in China and for the consideration of the sample size, we excluded *H Pylori* infection status as a criterion for participant inclusion or exclusion. Last, we used a self-administered questionnaire in Chinese rather than a validated questionnaire, making it possible that the participants cannot properly understand the questionnaire, though trained researchers had explained the questionnaire to them in advance.

Conclusions

Based on these findings, the study suggests that a symptom duration criterion of 3 months may be sufficient for diagnosing FD. Additionally, reducing the symptom onset frequency to no less than 1 day per week in the Rome IV criteria for PDS does not affect its postprandial symptom characteristics.

Table 5 Comparing symptom pattern between Rome IV criteria defined overlap-FD patients and potential overlap-FD patients

	Rome IV criteria defined overlap-FD	Overlap-FD with low symptom frequency				*P*			
Group	**1**	**2**	**3**	**4**	**5**	**1 vs. 2**	**1 vs. 3**	**1 vs. 4**	**1 vs. 5**
Symptom duration	**≥ 6 months**	**≥ 6 months**	**≥ 6 months**	**3-6months**	**3-6months**				
Symptom frequency (days per week)	**3–7**	**1**	**2**	**1**	**2**				
N	114	136	144	75	106				
Dyspepsia symptom									
Epigastric pain	74.6	87.5	80.6	80.9	76.2	**0.009**	0.249	0.134	0.739
Postprandial fullness	87.7	80.9	82.6	82.6	82.4	0.142	0.258	0.185	0.199
Early satiation	62.3	64.7	66.7	65.8	66.0	0.691	0.464	0.482	0.487
Epigastric burning	43.0	38.2	44.4	47.0	50.0	0.446	0.814	0.447	0.212
Dysmotility-like symptoms									
Any	79.8	51.5	81.3	68.4	79.3	**< 0.001**	0.774	0.017	0.908
Belching	64.0	42.6	66.7	57.7	67.2	**0.001**	0.659	0.220	0.554
Nausea	34.2	15.4	27.1	20.7	25.0	**0.001**	0.216	0.002	0.068
Vomiting	1.8	3.7	3.5	3.5	3.5	0.459	0.469	0.545	0.357
Reflux-like symptoms									
Any	29.8	32.4	27.8	28.6	25.8	0.667	0.718	0.798	0.419
Heartburn	9.6	22.8	11.8	16.5	10.5	**0.006**	0.580	0.069	0.793
Acid reflux	17.5	8.8	16.7	12.8	16.8	**0.040**	0.852	0.191	0.860
Non-acid reflux	5.3	3.7	1.4	2.1	1.6	0.542	0.144	0.066	0.093
Symptoms after meals						**0.047**	0.258	0.534	0.272
Aggravation	44.7	30.9	50.7	39.1	47.3				
Relief	26.3	27.2	29.2	30.0	31.3				
No change	28.9	41.9	20.1	30.9	21.5				
Overall symptom severity						0.055	**0.040**	0.810	0.054
Moderate	84.2	74.3	92.4	85.1	91.0				
Severe	15.8	25.7	7.6	14.9	9.0				

Potential overlap-FD patients are those who do not meet the Rome IV criteria solely because of the onset duration and/or the symptom onset frequency

The results of categorical variables were expressed as N%, Pearson's chi-square test or the Fisher exact test was used according to the analysis requirements. $P<0.05$ indicates a statistically significant difference

Abbreviations

BMI	Body mass index
EPS	Epigastric pain syndrome
FD	Functional dyspepsia
PDS	Postprandial fullness syndrome

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12876-024-03486-3.

Supplementary Material 1

Acknowledgements
Acknowledgment to all contributors who do not meet the criteria for authorship.

Author contributions
Study concept and design: Jinsheng Wang, Junhao Wu; Acquisition of data: Lei Zhang; Analysis and interpretation of data: Jinsheng Wang; Drafting of the manuscript: Jinsheng Wang; Critical revision of the manuscript for important intellectual content: Lei Zhang, Xiaohua Hou; Reviewed and approval of the final manuscript: Jinsheng Wang, Junhao Wu, Lei Zhang, Xiaohua Hou.

Funding
This study was funded by grants from the National Natural Science Foundation of China (NSFC), China (No: 81720108006, 81800463).

Data availability
Data available on request from the authors. Please contact the first author Jinsheng Wang (wangjinsheng@zju.edu.cn) or the corresponding author Lei Zhang (zhanglei2017@hust.edu.cn) if necessary.

Declarations

Ethics approval and consent to participate
Oral informed consent was obtained from all the included patients. Ethics Committee of Union Hospital of Tongji Medical College Huazhong University of Science and Technology approved this study.

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

Received: 21 March 2024 / Accepted: 29 October 2024
Published online: 05 November 2024

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