Assessment of the Asian Neurogastroenterology and Motility Association Chronic Constipation Criteria: An Asian Multicenter Cross-sectional Study

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Background/Aims
There is a need for a simple and practical tool adapted for the diagnosis of chronic constipation (CC) in the Asian population. This study compared the Asian Neurogastroenterology and Motility Association (ANMA) CC tool and Rome III criteria for the diagnosis of CC in Asian subjects.

Methods
This multicenter, cross-sectional study included subjects presenting at outpatient gastrointestinal clinics across Asia. Subjects with CC alert symptoms completed a combination Diagnosis Questionnaire to obtain a diagnosis based on 4 different diagnostic methods: self-defined, investigator’s judgment, ANMA CC tool, and Rome III criteria. The primary endpoint was the level of agreement/disagreement between the ANMA CC diagnostic tool and Rome III criteria for the diagnosis of CC.

Results
The primary analysis comprised of 449 subjects, 414 of whom had a positive diagnosis according to the ANMA CC tool. Rome III positive/ANMA positive and Rome III negative/ANMA negative diagnoses were reported in 76.8% and 7.8% of subjects, respectively, resulting in an overall percentage agreement of 84.6% between the 2 diagnostic methods. The overall percentage disagreement between these 2 diagnostic methods was 15.4%. A higher level of agreement was seen between the ANMA CC tool and self-defined (374 subjects [90.3%]) or investigator’s judgment criteria (388 subjects [93.7%]) compared with the Rome III criteria.

Conclusion
This study demonstrates that the ANMA CC tool can be a useful for Asian patients with CC.

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Key Words
Asia; Constipation; Cross-sectional studies; Humans; Practice guidelines as topic/standards
Introduction

Chronic constipation (CC) is a common disorder that can have a significant impact on the quality of life (QoL). The estimated prevalence of self-defined (SD) constipation in Asia (South Korea, China, and Indonesia) is 15-23% in women and approximately 11% in men. However, difficulty still exists in recognizing and establishing a diagnosis of CC. In a study of the Rome I diagnostic criteria, 66% of subjects with self-perceived CC and 71% of subjects with slow colonic transit times failed to meet the criteria. Furthermore, up to 65% of patients who met the criteria reported that they did not feel constipated.

The differing perceptions among physicians and patients regarding what constitutes constipation is another reason why the diagnosis of CC is such a challenge. Indeed, one study has reported that 27% of patients regarded a defecation frequency of once every 2 days as constipation, whereas the majority (73%) of physicians considered defeation once every 3 days as constipation. More recently, in a study of 26 patients with irritable bowel syndrome (IBS) from South Korea who considered that they were passing hard stools, only 7 met the definition of hard stool by the Rome III criteria (Bristol stool form scale type 1 or type 2).

These findings highlighted the need for a simple and practical tool adapted for the diagnosis of CC in the Asian population. As a result, the ANMA proposed a practical approach to the diagnosis of CC, which they called the ANMA CC tool. Diagnosis of CC using this tool adopts a two-step approach. In the first step, physicians are alerted to the possibility of CC by the presence of "alert symptoms" frequently associated with CC; these comprise of bloating, fullness, difficulty to pass stools, and the need for laxatives, as well as the usual constipation symptoms. In the presence of "alert symptoms," physicians ask the patient if they have experienced any of the 6 constipation symptoms in the Rome III criteria list on a regular basis; these consist of < 3 bowel movements per week, straining, the presence of lumpy or hard stools, the sensation of anorectal obstruction, the sensation of incomplete defeation, and manual maneuvers.

The aim of this study was to assess the agreement/disagreement between the ANMA CC tool and the Rome III criteria for the diagnosis of CC in Asian subjects consulting in gastroenterology clinics.

Materials and Methods

Study Design

The Constipation Symptoms Observational Study was a multicenter, cross-sectional, epidemiologic study that included primary and secondary care subjects presenting at 17 outpatient gastrointestinal clinics across Asia (China, South Korea, Malaysia, the Philippines, and Singapore). The study protocol was approved at each institution by an independent ethics committee or institutional review board, and was conducted in accordance with the Helsinki Declaration (ClinicalTrials.gov identifier: NCT01880294).

The study comprised of 2 stages. During Stage 1, all Asian subjects presenting with any condition at the participating clinics during investigator-chosen consecutive days (within a 3-month period) completed a screening worksheet incorporating the ANMA CC tool to determine the presence of CC alert symptoms. A maximum of 55 consecutive subjects were enrolled at each site, regardless of the number of consultation days chosen. At Stage 1, a question on the ANMA CC Tool worksheet was: “Do you think you have chronic constipation?” Patients who answered this question positively were considered to have a positive SD diagnosis of CC. Stage 2 was divided into 2 sub-stages. During Stage 2A, eligible subjects completed a combination Diagnosis Questionnaire (Appendix) to obtain a diagnosis of CC based on investigator’s judgment (INV), ANMA CC tool, and Rome III criteria. The Diagnosis Questionnaire also collected information on previous complementary examinations, Patient Assessment of Constipation Symptom (PAC-SYM) score and demographic details. Subjects with a positive diagnosis of CC based on the ANMA CC tool proceeded to Stage 2B, which involved the completion of a Documentation Questionnaire to collect additional information on the subject’s demographic details, medical history, history of CC, current symptoms of CC, comorbidities, and past and current medications for CC. Subjects who entered Stage 2B also completed the Patient Assessment of Constipation-Quality of Life (PAC-QOL) questionnaire.

Study Population

Eligible subjects were male or female Asian subjects (≥ 18 years of age) with ≥ 1 of the CC alert symptoms listed in the worksheet that was present for ≥ 3 months. Exclusion criteria included CC that was drug-induced or due to secondary causes, surgical obstruction, megacolon/megarectum, a diagnosis of pseudo-
obstruction or organic disorders of the large bowel. Female subjects who were pregnant were also excluded.

Evaluations

The primary endpoints were the proportion of subjects for whom the CC diagnosis according to the ANMA CC tool agreed with the diagnosis according to the Rome III criteria, and the proportion of subjects for whom the CC diagnosis according to the ANMA CC tool and the Rome III criteria did not agree.

Secondary endpoints were: (1) point prevalence rates for all diagnostic methods using the number of screened subjects as the denominator; (2) the concordance of the four diagnostic methods and agreement or disagreement on item levels of the different questionnaires; (3) analysis of the use of CC therapy; (4) analysis of the difference between investigator’s and subject’s judgment about CC diagnosis with regard to current symptoms and comorbidities; (5) PAC-SYM, and (6) PAC-QOL.

Statistical Methods

No formal sample size calculations were performed because of the exploratory nature of the study. It was anticipated that the screening of approximately 2000 consecutive subjects would be required to yield an estimated 400 subjects with suspected CC. The estimated sample size of 400 produced a two-sided 95% confidence interval (CI) with a width equal to 0.058 when the sample proportion was 0.1. For a sample proportion of 0.5, the width of the CI increased to 0.098 (exact confidence limit according Wilson).

The screening population was defined as all subjects who entered Stage 1. The screened positive population comprised of all subjects who scored positively for CC alert symptoms on the ANMA worksheet and provided informed consent. The positive ANMA diagnosis population was defined as all subjects from the screened positive population who had a positive diagnosis of CC according to the ANMA CC tool.

The descriptive analysis of nominal/ordinal data comprised of tabulation of frequency and percentages, continuous data of the mean, standard deviation, median, extreme values, and two-sided 95% CIs. Descriptive analysis of prior CC therapy for all subjects was also provided. There was no adjustment for multiplicity.

Results

A total of 4570 subjects entered Stage 1 of which 457 had ≥ 1 of the CC alert symptoms (Fig. 1). Eight subjects with secondary
or drug-induced CC were excluded. As a result, the primary analysis comprised of 449 subjects (ie, the screened positive population). Overall, 414 subjects had a positive CC diagnosis according to the ANMA CC tool and completed Stage 2B of the study (ie, the positive ANMA diagnosis population).

The majority of subjects were female (304 subjects [67.7%]) and Chinese (294 subjects [65.5%]) (Table 1). The overall mean (standard deviation) age and weight were 51.4 (16.4) years and 60.1 (9.6) kg, respectively.

**Primary Analysis**

The primary analysis was conducted on the screened positive population (n = 449). Twelve subjects with a Rome III positive (+)/ANMA negative (−) diagnosis were excluded because of anomalies in the timescale of symptom reporting, resulting in these patients failing to meet ANMA criteria, even though they were Rome III+. Overall, the proportions of subjects with Rome III+/ANMA+ and Rome III−/ANMA− diagnoses were 76.8% and 7.8%, respectively. Therefore, the overall agreement between the ANMA CC tool and Rome III criteria was 84.6% (380/449 subjects). The overall disagreement between these 2 methods (ie, a Rome III−/ANMA+ diagnosis) was 15.4% (69/449 subjects). Sensitivity analyses including the 12 Rome III+/ANMA− subjects who were excluded from the primary analysis did not show any relevant differences compared with the primary analysis (data not shown).

A total of 318 subjects had a positive diagnosis of CC using all 4 methods. A positive diagnosis using 3 out of the 4 methods was reported in 63 subjects, which included: 40 subjects who were ANMA+, SD+, INV+, and Rome III−; 14 subjects who were ANMA+, Rome III+, INV+, and SD−; and nine subjects who were ANMA+, Rome III+, SD+, and INV− (Table 2). Positive diagnoses of CC according to only 1 or 2 of the 4 methods were reported in 44 subjects. There were 24 subjects who passed the screening tool but who had a negative diagnosis on all 4 diagnostic methods.

### Prevalence of Chronic Constipation

In the total screening population (n = 4570), the prevalence of CC was: SD, 14.4%; ANMA CC tool, 9.1%; INV, 8.6%; and Rome III, 7.5% (Table 3). CC prevalence rates were higher in females than in males according to all diagnostic methods. In general, prevalence according to SD criteria was higher than the other 3 diagnostic methods due to the identification of SD CC within Stage 1, where 274 patients identified themselves as having SD CC but they did not report any CC alert symptom, and therefore did not progress to Stage 2A. Overall, within the screened population, 656 patients reported SD CC: 382 also reported ≥ 1 alert symptom and progressed to Stage 2A, and the remaining 274 reported no alert symptoms and were excluded.

### Concordance

A high level of agreement was seen between the diagnosis of CC according to the ANMA CC tool and SD or INV criteria (Fig. 2A). Most subjects who had a positive diagnosis of CC using the ANMA CC tool also had positive diagnoses according to SD (374 subjects [90.3%]) and INV (388 subjects [93.7%]) criteria. Similarly, the majority of the 35 ANMA− subjects were also SD− (27 subjects [77.1%]) and INV− (28 subjects [80.0%]) (Fig. 2A). As a result, the overall concordance was 89.3% between the ANMA CC tool and SD criteria, and 92.7% between the ANMA CC tool and INV criteria (Fig. 3A).

**Table 1.** Subject Demographics (Screened Positive Population, N = 449)

| All subjects | Mean age (yr [SD]) | 51.4 (16.4) |
| Gender (n [%]) | | |
| Female | 304 (67.7) |
| Male | 145 (32.3) |
| Mean BMI (kg/m² [SD]) | 22.8 (3.17) |
| Ethnicity (n [%]) | | |
| Chinese | 294 (65.5) |
| South Korean | 84 (18.7) |
| Filipino | 46 (10.2) |
| Malaysian | 11 (2.4) |
| Indian | 7 (1.6) |
| Other * | 7 (1.6) |

*Other ethnicities included Indonesian, Thai, Filipino-Chinese and Sabahan.

BMI, body mass index.

**Table 2.** Diagnosis of Chronic Constipation According to Various Diagnostic Methods (N = 449)

| Patients (n [%]) | CC self-defined | CC investigator | ANMA CC tool | CC Rome III criteria |
|---|---|---|---|---|
| 318 (70.8) | + | + | + | - |
| 40 (8.9) | + | + | + | - |
| 9 (2.0) | + | + | + | - |
| 14 (3.1) | + | + | + | - |

ANMA, Asian Neurogastroenterology and Motility Association; CC, chronic constipation.
The majority of the 345 subjects who had a positive diagnosis of CC according to the Rome III criteria also had positive diagnoses according to SD (327 subjects [95.0%]) and INV (332 subjects [96.2%]) criteria (Fig. 2B). Overall concordance was 83.7% between the Rome III and SD criteria, and 83.1% between the Rome III and INV criteria (Fig. 3A). In contrast to the findings in ANMA− subjects, < 50% of the 104 Rome III− subjects were SD− (49 subjects [47.1%]) or INV− (41 subjects [39.4%]) (Fig. 2B).

### Table 3. Prevalence (%) of Chronic Constipation According to Different Diagnostic Methods (Screening Population, N = 4570)

|                      | ANMA CC tool | CC Rome III criteria | CC investigator-defined | CC self-defined |
|----------------------|--------------|-----------------------|-------------------------|-----------------|
| Total (N = 4570)     | 9.1          | 7.5                   | 8.6                     | 14.4            |
| Gender               |              |                       |                         |                 |
| Male (n = 1993)      | 6.1          | 4.6                   | 5.8                     | 10.9            |
| Female (n = 2577)    | 11.3         | 9.9                   | 10.9                    | 17.0            |
| Country              |              |                       |                         |                 |
| China (n = 3225)     | 6.9          | 5.9                   | 6.8                     | 14.3            |
| South Korea (n = 450)| 18.4         | 14.2                  | 16.0                    | 21.3            |
| Malaysia (n = 540)   | 7.2          | 6.3                   | 6.9                     | 8.1             |
| Philippines (n = 271)| 18.1         | 15.5                  | 17.7                    | 17.7            |
| Singapore (n = 84)   | 23.8         | 19.0                  | 21.4                    | 9.5             |

ANMA, Asian Neurogastroenterology and Motility Association; CC, chronic constipation.
3B). Therefore, a large proportion of Rome III− subjects had a positive diagnosis of CC according to the SD or INV criteria.

**Patient Assessment of Constipation**

**Symptoms scores (Patient Assessment of Constipation Symptom)**

Mean (standard deviation) total PAC-SYM scores were similar in Rome III+ and ANMA+ subjects (1.44 [0.61] vs 1.35 [0.63]) (Fig. 4A). PAC-SYM abdominal subscale scores were similar between CC-positive and CC-negative subjects according to both the ANMA CC tool and Rome III criteria, whereas stool and rectal symptom scores were more than double in subjects with CC. Mean (standard deviation) stool symptom scores were, for Rome III+ vs Rome III− (Fig. 4A): 1.96 (0.82) vs 0.86 (0.64) and for ANMA+ vs ANMA−: 1.81 (0.85) vs 0.43 (0.42). Mean (standard deviation) rectal symptom scores were, for Rome III+ vs Rome III− (Fig. 4A): 0.84 (0.84) vs 0.34 (0.55) and for ANMA+ vs ANMA−: 0.77 (0.82) and 0.24 (0.40).

**Previous Chronic Constipation Therapy**

Of the ANMA+ subjects who entered stage 2B of the study, 271 (65%) had received CC treatment in the three months before the study. Of these, 80% had used one or more pharmacological treatment. Seventy-six percent had used one or more non-pharmacological treatment, and 29% had used one or more alternative therapy. Of the subjects who used a pharmacological therapy, 26% only used pharmacological therapy, 48% combined it with a non-pharmacological therapy, and 24% combined it with a non-pharmacological therapy and an alternative therapy.

Of the subjects who used a pharmacological therapy, the most commonly used were osmotic laxatives (56%), stimulant laxatives (35%), prokinetics (23%), and probiotics (20%).

Of the subjects who used a non-pharmacological therapy, the most commonly used were increased fiber intake (76%) and diet modification (75%). Of subjects who used an alternative therapy, 94% used traditional or herbal medicines.

**Difference between investigator’s and subject’s judgment about chronic constipation diagnosis**

With regard to current symptoms and co-morbidities, disagreement was observed in only 7% (33/449) cases where the investigator reported a positive response and the patient reported negative. Furthermore, only 4% (20/449) cases were recorded where the investigator reported a negative response and the patient reported positive. However, for patients who thought they had CC but did not screen positively, the agreement with the investigator would probably be much lower.

**Quality of life scores (Patient Assessment of Constipation-Quality of Life)**

The PAC-QOL questionnaire was completed by 414
ANMA+ subjects (Fig. 4B). Mean PAC-QOL total scores were similar in Rome III+ and ANMA+ subjects (1.53 [0.67] vs 1.45 [0.67]). Overall, mean scores were significantly lower among subjects who were ANMA+ but Rome III– (1.09 [0.55]; n = 69; $P < 0.0001$, Wilcoxon-2-sample test).

**Discussion**

The ANMA criteria are based on the Rome III assessment, with the primary difference being a pre-diagnostic alert symptom checklist with the ANMA test. In all other regards the CC symptoms are identical between the ANMA and Rome III criteria; however, the minimum criteria for a positive diagnosis are lower with the ANMA test where one symptom and only 3 months’ duration are required. The requirement for a single symptom is reinforced by the pre-diagnostic alert entry step, and the 3 month symptom duration is based on uncertainty with regards to the accuracy of recall beyond 3 months. These considerations are important when it is remembered that the ANMA criteria are intended for day-to-day clinical management within primary and secondary care, and not for academic research or for recruitment of patients for specialized treatments, such as biofeedback and surgery.

The primary objective of this study was to assess agreement/disagreement between the ANMA CC tool and Rome III criteria (ie, the western “gold standard”) for the diagnosis of CC in Asian subjects. The agreement between the Rome III criteria and the ANMA CC tool indicated that 76.8% of subjects had a Rome III+/ANMA+ diagnosis and 7.8% had a Rome III–/ANMA– diagnosis, resulting in an overall agreement of 84.6% and disagreement of 15.4%. These findings demonstrate that diagnosis of CC based on the ANMA CC tool agrees with that of Rome III criteria in the majority of Asian subjects with CC alert symptoms.

There are variations in the prevalence and symptoms of CC between East and West and also amongst countries within Asia which complicate the implementation of a standardized diagnostic approach. For instance, patients from Asia have a shorter colonic transit time than Western patients, and in South Korea most patients who experience hard stools do not meet Rome criteria for hard stools. There are also differences within Asia; in India, patients with self-perceived constipation report a median of 2 bowel movements per day and in China, where there are marked regional differences in the prevalence of constipation. Similarly, and as observed in our results, there are slight differences in the prevalence of CC among Malays, Indians, and Chinese in Singapore.

A more reliable and accurate diagnosis of CC is required to aid in the optimal management of this disease. However, there is often
disagreement between how patients and physicians define CC, with patients focusing on symptoms rather than stool frequency.1,3 This suggests that patients are currently underdiagnosed by existing criteria. In the current study, concordance was high for a positive diagnosis of CC based on the ANMA and Rome III criteria. This study also shows that a positive diagnosis with either tool is in concordance with a positive SD and INV diagnosis. The majority of ANMA- subjects were also SD- and INV-. In contrast, a high proportion of Rome III- subjects were SD+ and/or INV+, suggesting that the Rome III criteria may have failed to detect a substantial proportion of subjects who were considered to have CC according to themselves or by an investigator. Therefore, these results indicate that the ANMA CC tool correlates more closely with both subject- and INV CC, compared with Rome III criteria.

Two factors, duration of symptom assessment and differences in diagnostic criteria, may explain the differences between the ANMA CC and Rome III populations, and how these correlate with SD and INV CC criteria. Firstly, the duration of symptom onset for diagnosis using the ANMA CC tool is 3 months, which is shorter than the 6-month duration for Rome III criteria (ie, criteria fulfilled for the past 3 months with symptom onset ≥ 6 months prior to diagnosis). To offset this potential difference, we used a 3-month observation period for all diagnostic methods to ensure that consistent symptom profiles were captured within each tool. It would also be of interest to determine the proportion of ANMA+ patients with symptoms for < 6 months vs ≥ 6 months; however, these data were not collected within the current protocol and thus further analysis is not possible. Secondly, the ANMA tool utilizes broader diagnostic criteria than the Rome III tool. As a result of these differences, there may be a potential for overlap between CC and constipation-subtype IBS (IBS-C) when using the ANMA CC tool, whereas the Rome III criteria may more clearly differentiate CC from IBS-C. However, opposing this theory, a recent study has highlighted the difficulty in distinguishing between CC and IBS-C using Rome III criteria.15,16 Furthermore, it has been suggested that both CC and IBS-C are part of the same condition,16 and similar therapeutic strategies are often utilized. Ultimately, further study is required to assess the differential diagnoses in those patients who are Rome III- but ANMA+.

CC prevalence rates reported in this study were variable between the different diagnostic methods and countries. The prevalence of CC in China and South Korea was higher when SD, compared with that of Singapore, where prevalence of SD CC appeared to have a much lower frequency than INV CC or a positive diagnosis according to the ANMA CC tool and Rome III criteria. This may have been because patients from Singapore were recruited from a single center in a private healthcare institution comprising of primary and secondary care level patients. Garrigues et al17 also reported differences in the prevalence of CC according to self-reported, Rome I, and Rome II criteria. Differences in prevalence among Asian countries have also been previously reported using SD criteria.1 Furthermore, the higher prevalence rates of CC in female versus male subjects in the current study is consistent with those in North America, Europe, and Oceania.20,21

The symptoms of CC are unpleasant and have an adverse effect on patients’ QoL.19,22 In the present study, PAC-QOL scores were similar between ANMA+ and Rome III+ subjects, but tended to be lower in ANMA+/Rome III- subjects suggesting that when defined by one tool only ie, less broad criteria, a difference may be more apparent. Therefore, consistent QoL findings were seen in subjects with agreement between the 2 diagnostic methods. An interesting observation was the very low symptom scores seen in patients who were ANMA-. This is consistent with the broad criteria used in the ANMA assessment and hence its ability to detect patients with very mild symptoms that may not be detected as CC-positive by the more stringent Rome III criteria. Therefore, the use of the ANMA CC tool offers the opportunity to detect patients with milder forms of CC and those in whom symptoms have not progressed to a severe stage. Furthermore, in a recent clinical trial of prucalopride, improvements in PAC-SYM and PAC-QOL subscales was associated with improved symptoms among Asian and non-Asian patients with CC. This was evident in patients in both active and placebo treatment arms.24

In conclusion, a high level of agreement was seen for the diagnosis of CC according to the ANMA CC tool and Rome III criteria in Asian patients with CC alert symptoms. Furthermore, the ANMA CC tool demonstrated higher agreement with both SD and INV criteria than Rome III criteria. Therefore, the ANMA CC tool appears to be more sensitive than Rome III criteria for diagnosing CC in Asia patients. Further prospective studies are warranted to confirm the applicability of the ANMA CC tool in a wider Asian population.

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