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DOI:
10.1007/s10620-018-5419-3

Health Care Providers Underestimate Patient Reported Glucocorticoid Use in Crohn's Disease

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Running head title: Underestimated Glucocorticoid Use in Crohn's

Word count (text only, without title, authors, abstract, tables, statements of interest, and references): 2412

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Statement of interests

Declaration of personal interests

S Ghosh has served on ad-hoc advisory boards of AbbVie, Merck, Shire, Pfizer, Receptos, Novo-Nordisk, Bristol Myers Squibb and Janssen. He has received honoraria for lecturing in educational events from AbbVie, Merck, Janssen, Takeda and Shire, and has received research support from AbbVie and Merck.

B Bressler is a consultant for AbbVie, Actavis, Jansen, Shire, Genentech, Takeda, Pendopharm, Celltrion; served on the Speaker's Bureau for AbbVie, Jansen, Takeda, Shire, Ferring, Actavis; received research/educational support from AbbVie, Jansen, Millenium, Bristol-Myers Squibb,

Amgen, GSK, Genentech, Celgene, AstraZeneca, RedHill Biopharm, Alvine, and BI, and has stock options from Qu Biologics.

J Petkau has nothing to disclose.

RB Thakkar and M Skup are employees of AbbVie and may hold stock. J Chao and S Wang were employees of AbbVie at the time of research and may own AbbVie stock.

R Panaccione served as a consultant for AbbVie, Amgen, Aptalis, AstraZeneca, Baxter, Eisai, Ferring, Jansen, Merck, Schering-Plough, Shire, Centocor, Elan, Glaxo-Smith Kline, UCB, Pfizer, Bristol-Myers Squibb, Warmer Chilcott; served on the Speaker's Bureau for AbbVie, AstraZeneca, Jansen, Schering-Plough, Shire, Centocor, Elan, Prometheus, and Warner Chilcott; served on advisory boards for AbbVie, Amgen, Aptalis, AstraZeneca, Baxter, Eisai, Ferring, Jansen, Merck, Schering-Plough, Shire, Centocor, Elan, Glaxo-Smith Kline, UCB, Pfizer, Bristol-Myers Squibb, Warmer Chilcott; and received research/educational support from AbbVie, Ferring, Jansen, Schering-Plough, Centocor, Millenium, Elan, Proctor and Gamble, and Bristol-Myers Squibb.

S Schreiber served as study investigator and consultant for AbbVie and has participated in continuing medical education events supported by unrestricted educational grants from AbbVie. He has also served as a consultant and as a lecturer for Centocor/MSD, Schering-Plough, UCB and Shire.

Specific author contributions

S Ghosh planned and conducted the study, collected data, reviewed the manuscript, made substantial content suggestions, and approved the final draft.

B Bressler conducted the study, collected data, interpreted data, reviewed the manuscript, made substantial content suggestions, and approved the final draft.

J Petkau conducted the study, collected data, interpreted data, reviewed the manuscript, made substantial content suggestions, and approved the final draft.

RB Thakkar interpreted data, reviewed the manuscript, made substantial content suggestions, and approved the final draft.

M Skup conducted the data analyses, interpreted data, reviewed the manuscript, made substantial content suggestions, and approved the final draft.

S Wang conducted the data analyses, interpreted data, reviewed the manuscript, made substantial content suggestions, and approved the final draft.

J Chao conducted the data analyses, interpreted data, reviewed the manuscript, made substantial content suggestions, and approved the final draft.

R Panaccione conducted the study, collected data, interpreted data, reviewed the manuscript, made substantial content suggestions, and approved the final draft.

S Schreiber conducted the study, collected data, interpreted data, reviewed the manuscript, made substantial content suggestions, and approved the final draft.

Declaration of funding interests

This study was funded in full by AbbVie, North Chicago, Illinois, which is represented by R Thakkar, S Wang, M Skup and J Chao. AbbVie was involved in developing the study concept and participated in the analysis and interpretation of the data; preparation, review and approval of the manuscript; and decision to submit the manuscript for publication.

Abstract [Limit 250 words, currently 249]

Background: One of the therapy goals for Crohn's disease (CD) is glucocorticoid-free remission. Studies have shown care setting-specific variations in inflammatory bowel disease (IBD) management.

Aims: The principal objective of this study was to assess concordance between patient-reported and physician-reported outcomes in two different care settings (IBD centers and community practices).

Methods: Overall and long-term (≥3 months) glucocorticoid, immunosuppressant and biologics use in participants ≥18 years old with a confirmed diagnosis of CD were collected. HCPs were grouped by inflammatory bowel disease (IBD) centers and community practices. Quality of life (using EuroQol 5D [EQ-5D]) and work/activity days lost were assessed. Agreement between patients' and HCPs' responses to survey questions was tested using kappa statistics.

Results: Data from 812 patients were examined. Significantly more patients vs. HCPs reported oral glucocorticoid use (25.9% vs. 20.8%, kappa=0.735, *P*<0.0001). Long-term use of oral glucocorticoids was similar for patients vs. HCPs (67.7% vs. 63.8%, kappa=0.598, p=0.53). Immunosuppressant use was 52.4% vs. 51.1% (kappa=0.784) and biologics use was 49.5% vs. 47.0% (kappa=0.909) for patients vs. HCPs. Patients and HCPs reported greater rates of symptom improvement with vs without biologic therapy (patients: 33.3% vs 16.8%; HCPs: 29.3% vs 13.5%, both *P*<0.001). Patients with vs. without routine follow-up were less likely to be treated with long-term glucocorticoid monotherapy (10.3% vs. 20.7%, *P*<0.01) and had fewer lost work/activity days (5 vs. 8 days, *P*<0.05).

Conclusions: Routine follow-up and higher rates of biologic use are associated with improvement in disease symptoms and general health among patients with Crohn's disease.

Keywords: Crohn's disease; glucocorticoids; patient-reported outcomes; physician-reported outcomes; quality of life

Introduction

Crohn's disease (CD) is a chronic gastrointestinal (GI) inflammatory condition with potentially debilitating symptoms that can lead to serious complications, disabilities and reduced quality of life.[1-5] CD affects substantial numbers of patients worldwide, with prevalence of 322 per 100,000 persons in Europe and 319 per 100,000 persons in North America.[6]

Therapy for CD depends on the location and severity of the disease, as well as any disease-associated complications.[7,8] Treatment may include aminosalicylates, glucocorticoids, immunomodulators, tumor necrosis factor antagonists, other biologics such as integrin blockers and IL-12/23 p40 inhibitors, and/or surgery.[8-10] Glucocorticoid therapy has been shown to induce remission in patients with moderate to severe CD.[11-15] However, glucocorticoid therapy is associated with a number of serious side effects, including osteoporosis, glaucoma, cataracts, hypertension, diabetes and increased risk of infections,[16-23] which makes the long-term use of glucocorticoids undesirable. Thus, while it may be necessary to use glucocorticoid therapy to rapidly induce remission and/or quickly reduce moderately severe or severe CD symptoms associated with acute flares, one of the goals of CD therapy is glucocorticoid-free remission.

Studies have shown country-specific and care setting-specific variations in inflammatory bowel disease (IBD) care.[24-27] This variation can lead to differences in quality of care and clinical outcomes. Information on the rates of important outcomes of disease control, such as

glucocorticoid-free remission, CD-related surgery and hospitalization, and patients' quality of life in IBD centers or in real-life practice, is limited.

The principal objective of this study was to assess concordance between patient-reported and physician-reported data from centers in two different practice settings: community practice and IBD center. Patient-reported outcome measures included rates of glucocorticoid-free remission (defined as no glucocorticoid use in the 3 months before the survey was conducted), CD-related hospitalization and surgery, patients' general quality of life, and days lost from work or inability to perform normal activities because of CD.

Methods

Study Design

This was a cross-sectional study using a paper-based questionnaire, POLARIS (**P**ractice Patterns with Inflammat**O**ry Bowel Disease Hea**L**th C**AR**e Assessment Quest**I**onnaire**S**), administered to patients and their HCPs. Patients and their HCPs completed their questionnaires on the same day, separately. The questions were designed to obtain information about the course of CD, the level of CD-related symptoms, patient characteristics and treatment information. The study was conducted from July 11, 2012 to November 28, 2012.

Patients

Patients ≥18 years old with a confirmed diagnosis of CD, disease duration ≥1 year, and ≥2 visits with a participating HCP (consulting gastroenterologist, nurse practitioner, or physician's nurse)

at IBD centers and community practices in Canada and Germany were eligible to participate in the study. IBD centers were specialized patient care centers that were part of a network of cooperating practices with physicians who focus on diagnostic and treatment services for individuals with IBD.[28] A diagnosis of CD was confirmed by endoscopy, radiologic evaluation, histology or surgical pathology (or investigator's discretion if some of these details were not available).

Ethical considerations

The study protocol was approved by independent Medical Research Ethics Committees in agreement with local legal requirements in Canada and Germany. All patients provided written informed consent before participating in the study. Consenting patients were also asked to sign and date a form indicating that they were willing to have their HCP supply additional information about their condition and their current and previous CD treatment. To protect disclosure of patient identities, a unique identification number was assigned to each patient before collection of data; this identification number was used on both the patient and HCP questionnaires. No patient identifiable information was included in any of the information collected.

Questionnaires

The HCP and patient questionnaires are included in Appendix 1 and Appendix 2, respectively. HCPs were asked when each patient was diagnosed with CD, where the disease was located, whether the patient had upper GI disease or perianal disease, and whether the patient received

therapy with biologics or immunosuppressants during the year before the survey was conducted. HCPs were also asked whether their patients received any oral glucocorticoid monotherapy (excluding budesonide) or glucocorticoids in combination with other therapies and the length of use during the year before the survey was conducted. HCPs were asked if their patients were hospitalized for reasons related to CD and if their patients had undergone CD-related surgery (i.e. laparotomy or fistula drainage) in the year before the survey was conducted. The HCP questionnaire also contained questions about patient referral source and frequency of HCP follow-up. Finally, HCPs were asked to select a statement along with a disease symptoms curve that best represented the course of the patient's disease over the past 12 months before the questionnaire was completed: improvement (a decrease in the severity of bowel symptoms during the previous year), worsening (an increase in the severity of bowel symptoms during the previous year), continuous and severe bowel symptoms, periods of relapse and periods of severe symptoms, or no symptoms or very mild symptoms throughout the past year.

The patient's questionnaire asked for the patient's age; sex; smoking history; use of medications, including oral glucocorticoid use; length of medication use during the year before the questionnaire was completed and how often they had routine follow-up appointments. The disease statement and symptom curve given to the HCPs was included. Patients were also asked whether they had been in the hospital or had surgery because of their CD in the year before completing the survey. To assess general quality of life, patients were asked to complete the EQ-5D questionnaire. The minimally important difference for the EQ-5D utility is

approximately 0.08 (range: 0 = worst health scenario to 1.0 best health scenario), and higher scores represent better quality of life.[29] Patients were asked to rate their health state at the time of the survey on a scale of 0 to 10, where 0 represented the worst imaginable health state and 10 the best imaginable health state. Patients were also asked how many days they had not been able to work or go about their normal activities because of their CD during the month before completing the questionnaire. Brand names of biologics and azathioprine, mercaptopurine, and methotrexate were provided to patients to facilitate recall and minimize bias. Budesonide and its brand name were also provided, although budesonide was not counted in glucocorticoid use in this survey. The brand names of other glucocorticoids were not provided; however, the research coordinator who handed out the survey was available to answer any questions or provide clarification to patients at the time the survey was completed.

Only paired surveys were included in the study. Patients and HCPs were blinded to each other's response. HCPs were aware that patients would be completing a questionnaire but were not aware of the exact nature of the questions.

Data analysis

Demographics and disease characteristics of the surveyed population as well as CD treatment patterns, measures of symptoms and disease control were summarized using descriptive statistics. Outcomes, including referral source, glucocorticoid sparing medications (i.e. anti-TNF biologics, immunosuppressants), glucocorticoid use, disease course and selected patient-reported outcomes, were evaluated and compared by the type of facility (IBD center or

community practice), whether the patients had routine follow-up, and whether the patients received biologic therapy.

Chi-square tests and *t*-tests were used to determine differences between groups for categorical and continuous variables, respectively. For quality of life assessments, differences between groups were assessed using analysis of variance. Agreement between patients' and HCPs' responses to survey questions was tested and inter-rater agreement was evaluated using Cohen's kappa statistics. The literature has proposed the following for strength of agreement for the kappa coefficient: 0–0.20 as slight, 0.21–0.40 as fair, 0.41–0.60 as moderate, 0.61–0.80 as substantial and 0.81–1 as almost perfect agreement.[30]

Results

Study population

A total of 809 HCPs (430 in Canada and 379 in Germany) and corresponding 812 CD patients were identified. Questionnaires were completed and analyzed by 798 (98.3%) patients and 809 (100%) HCPs. There were 560 (69.0%) patients seen by HCPs in IBD centers and 252 (31.0%) patients in community practices. The average age of the study population was 41 years and 55.3% were women (**Table 1**). Patients who responded to the questionnaire reported that they had CD for approximately 14 years on average. Most patients had ileocolonic CD without upper GI disease or perianal disease.

Different patterns were observed regarding the patient referral source at IBD centers vs. community practices. At IBD centers, approximately half of the patients (53.2%) were self-presenting or referred by a general practitioner and the other half (46.8%) were referred by a specialist or surgeon. In contrast, at community practices 92.3% of patients were self-presenting or referred by a general practitioner and only 7.7% were referred by a specialist or surgeon. Although there were differences in the patient referral source, the mean disease duration since diagnosis was similar between patients at IBD centers and community practices.

Use of oral glucocorticoids

Significantly more patients vs. HCPs reported any oral glucocorticoid use (as monotherapy or combined with other therapies) (25.9% vs. 20.8%, kappa = 0.735, $P<0.0001$). Patients vs. HCPs reported also on the use of glucocorticoids as follows: oral glucocorticoid monotherapy (4.4%

vs. 3.7%, kappa = 0.514, p=0.26); long-term (≥3 months continuous use) use of any oral glucocorticoid including monotherapy or therapy combined with other therapies (67.7% vs. 63.8%, kappa = 0.598, p=0.53); and long-term (≥3 months continuous use) use of oral glucocorticoid monotherapy (11.6% vs. 7.2%, kappa = 0.433, p=0.74) (Figure 1). Agreements between patients and their HCPs were much lower in community practices than in IBD centers in all glucocorticoid use measures: use of any oral glucocorticoid (kappa = 0.609 vs. 0.781), use of oral glucocorticoid monotherapy (0.425 vs. 0.575), long-term (≥3 months) use of any oral glucocorticoid (0.263 vs. 0.663), and long-term (≥3 months) use of oral glucocorticoid monotherapy (0.250 vs. 0.520).

Use of glucocorticoid-sparing medications

Overall, responses from patients and their HCPs were similar regarding use of immunosuppressants (52.4% vs. 51.1%, kappa = 0.784; Figure 2) and biologics (49.5% vs. 47.0%, kappa=0.909; Figure 3), with lower agreements observed in community practices than in IBD centers (use of immunosuppressants: kappa = 0.715 vs. 0.807; use of biologics: kappa = 0.861 vs. 0.928).

Improved disease course during the past year

HCPs at IBD centers reported that a greater percentage of their patients had improvement in CD-related symptoms compared with HCPs at community practices (26.1% vs. 9.2%, *P*<0.001; Figure 4). HCPs also reported greater rates of symptom improvement among patients who received biologics compared with those who did not receive biologics (29.3% vs. 13.5%,

P<0.001). Patients who received biologic therapy were also more likely to report that their health had improved during the past year compared with patients not receiving biologics (33.3% vs. 16.8%, *P*<0.001). In addition, moderate to high agreement was observed (63.5% [502/790]) between HCPs and patients in reporting the change of the disease course.

Overall, HCPs reported fewer CD-related hospitalizations (13.2% vs. 19.5%, *P*<0.0001) and fewer CD-related surgeries (6.2% vs. 10.6%, *P*<0.0001) during the past year than their patients. HCPs at IBD centers reported more CD-related hospitalizations (15.7% vs. 8.0%; *P*=0.003) and more CD-related surgeries (7.0% vs. 4.4%; *P*=0.16) compared with HCPs at community practices.

Quality of life and health state in patients with and without routine follow-up

On the IBD health care assessment questionnaire, patients were asked how often (i.e. every 3 months, every 6 months, every year, or do not have routine follow-up appointments) they attended the IBD clinic for routine follow-up appointments. Patients treated at community practices were more likely to report that they did not have routine follow-up appointments with their HCPs compared with those treated at IBD centers (30.9% vs. 8.6%; *P*<0.01). Significantly greater quality of life, as assessed by higher mean EQ-5D scores (0.8 vs. 0.7, *P*<0.01) and higher patient mean health state scale scores (7.1 vs. 6.3, *P*<0.01), were observed in patients with routine follow-up vs. those without routine follow-up. In addition, significantly fewer work/activity days (median: 5 days vs. 8 days, *P*<0.05) were lost among patients with routine follow-up vs. those without routine follow-up care. Patients who received routine

follow-up were also less likely to be treated with long-term glucocorticoid monotherapy than those who did not have routine follow-up (10.3% vs. 20.7%, *P*<0.01).

Discussion

In this cross-sectional study, we assessed treatment patterns, quality of care and level of disease control in IBD centers and community practices from the perspective of patients with CD and their HCPs. We found that use of agents that provide alternatives to long term use of glucocorticoids (oral immune suppressants and anti-TNF therapy) was relatively high, particularly at IBD centers in which more than half of the patients were receiving these agents. The frequency of patients receiving long-term glucocorticoid monotherapy was lower in IBD centers compared with community practices. The higher use of glucocorticoid-sparing treatments to reduce adverse effects associated with long-term glucocorticoid use in IBD centers is consistent with current guidelines on the treatment of CD.[31]

Results of this cross-sectional survey revealed discordance between patients' self-reports and their HCPs' documentation regarding use of glucocorticoids. This discordance in the reporting of oral glucocorticoid use was more marked in community practices than in IBD centers. There are at least two possible explanations for the discrepancy. First, HCPs may underestimate the extent of long-term glucocorticoid therapy by their patients, and second, patients may self-medicate with glucocorticoids. Either way, these findings suggest that communications between patients and HCPs may be suboptimal in certain instances. Improvements in care,

including routine follow-up and enhanced communication during visits, may serve to improve discordance. Currently, standards are being set to reduce variation in the quality of care.[32,33]

Patients treated with biologics were in better symptomatic disease control in comparison with those not receiving biologics. Regular routine follow-up appointments were more common for patients treated in IBD centers and patients receiving routine follow-ups appeared to have a lower frequency of long-term glucocorticoid monotherapies, better quality of life, improvement in symptoms and fewer work/activity days lost during the month before completing the questionnaire. The best care for patients with CD may come from IBD centers where a team of individuals specializing in different aspects of treatment is available to meet the needs of different patients, or of a single patient, as treatment needs over time change.[34,35]

Results of this survey need to be interpreted while keeping in mind possible sources of bias. There is currently no standard definition of what constitutes an IBD center. In our study, the centers were identified as an IBD center or a community practice by the principal investigators in the countries (Canada and Germany) where the survey was conducted. There might be variation in clinical practice and HCP/patient behavior between the two countries. It is possible that patients treated at IBD centers have more severe disease and therefore receive more aggressive treatment than those at community practices, which may explain why a greater percentage of patients had CD-related hospitalizations and CD-related surgeries at IBD centers compared with patients being treated at community practices. The survey did not collect

information on strictures and non-perianal fistula, so we are not able to comment on these complications.

In summary, results of this cross-sectional survey showed that patients who received more routine monitoring of their disease progression had greater symptom relief and had fewer lost work or activity days.

Acknowledgements

Writing support was provided by Joann Hettasch, PhD, of Fishawack Facilitate Ltd, Conshohocken, PA, and was funded by AbbVie, Inc., North Chicago, IL.

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Tables

Table 1. Baseline demographics and clinical characteristics of patients with Crohn's disease

Characteristic	IBD Center	Community Practice
	(N = 560)	(N = 252)
Age		
N	560	249
Mean ± SD, years	39.8 ± 14.3	42.3 ± 13.7
Sex		
N	560	249
Women, n (%)	302 (53.9)	145 (58.2)
Smoking status		
N	559	249
Current, n (%)	108 (19.3)	72 (28.9)
Former, n (%)	174 (31.1)	101 (40.6)
Never, n (%)	277 (49.6)	76 (30.5)
Years since CD diagnosis (per physician)		
N	558	251
Mean ± SD	13.2 (10.2)	14.3 (8.7)
Disease location[a]		
N	560	252
Terminal ileum, n (%)	391 (69.8)	175 (69.4)

Colon, n (%)	389 (69.5)	213 (84.5)
Jejunum/ileum, n (%)	39 (7.0)	23 (9.1)
No location checked, n (%)	3 (0.5)	3 (1.2)
Upper GI disease?		
N	552	251
Yes, n (%)	47 (8.5)	17 (6.8)
No, n (%)	490 (88.8)	231 (92.0)
Not sure, n (%)	15 (2.7)	3 (1.2)
Perianal disease?		
N	552	250
Yes, n (%)	135 (24.5)	40 (16.0)
No, n (%)	409 (74.1)	209 (83.6)
Not sure, n (%)	8 (1.4)	1 (0.4)
Referral, n (%)		
N	545	243
Self-presenting	82 (15.1)	117 (48.2)
General practitioner	233 (42.8)	89 (36.6)
Specialist	199 (36.5)	25 (10.3)
Surgeon	31 (5.7)	12 (4.9)

CD, Crohn's Disease; GI, gastrointestinal; IBD, inflammatory bowel disease.

[a]HCP could select all disease locations that applied.

Figure legends

Figure 1. Reported use of oral glucocorticoids (excluding budesonide) during the past year: (A) Any oral glucocorticoid use (monotherapy or combined with other therapies), (B) Oral glucocorticoid monotherapy use, (C) Any long-term (≥3 months) oral glucocorticoid use (monotherapy or combined with other therapies) among any oral glucocorticoid users, (D) Long-term (≥3 months) oral glucocorticoid monotherapy use among any oral glucocorticoid users. Missing values were not imputed. *P*-values derived from McNemar test.

Figure 2. Reported use of oral immunosuppressants during the past year. Immunosuppressants included azathioprine, 6-mercaptopurine and methotrexate. Missing values were not imputed.

Figure 3. Reported use of anti-TNF biologics during the past year. Biologics included infliximab, adalimumab and certolizumab. Missing values were not imputed.

Figure 4. Improved disease course of CD patients during the past year as reported by HCPs. Missing values were not imputed.

Figure 1A

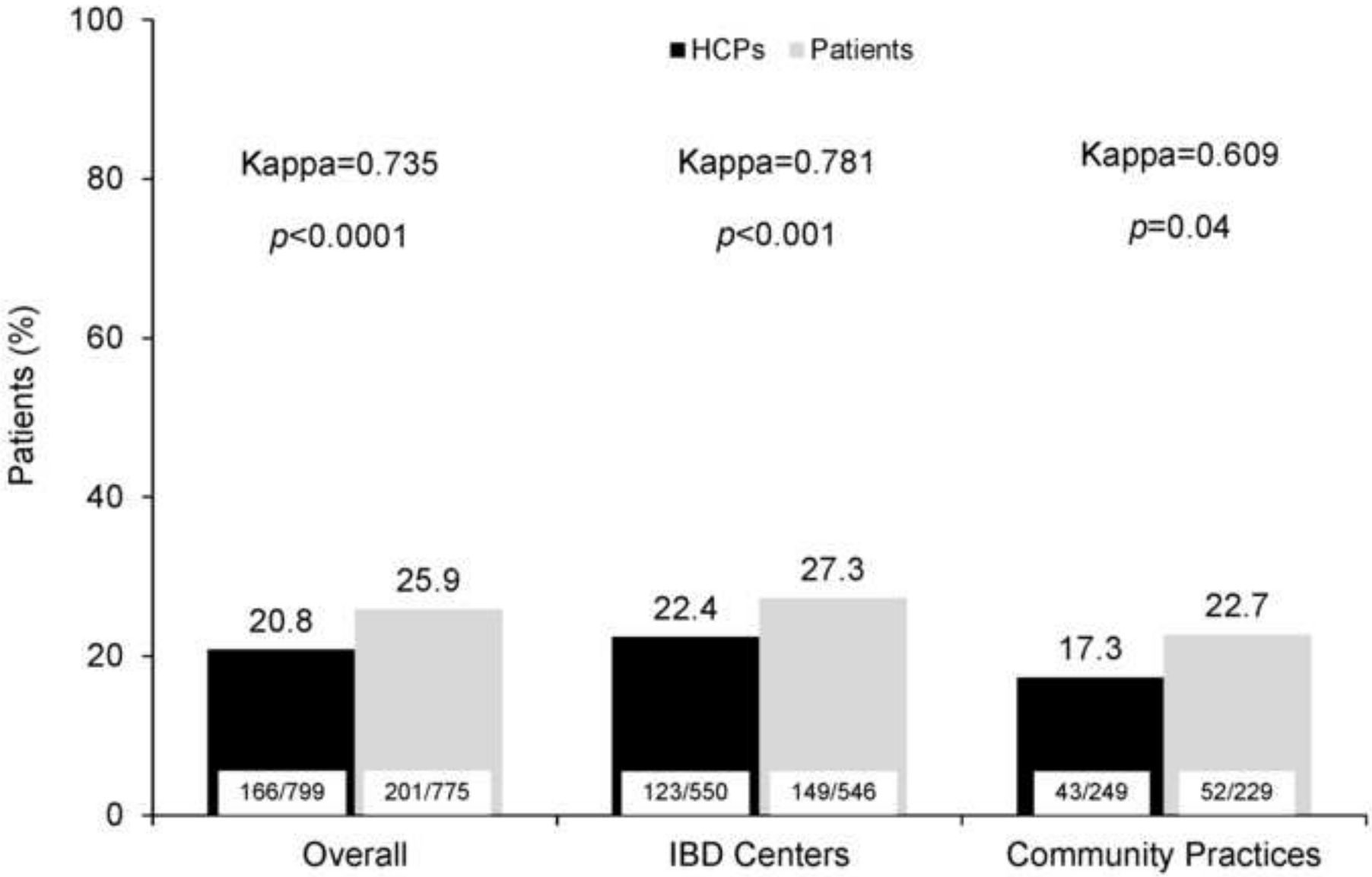

Figure 1B

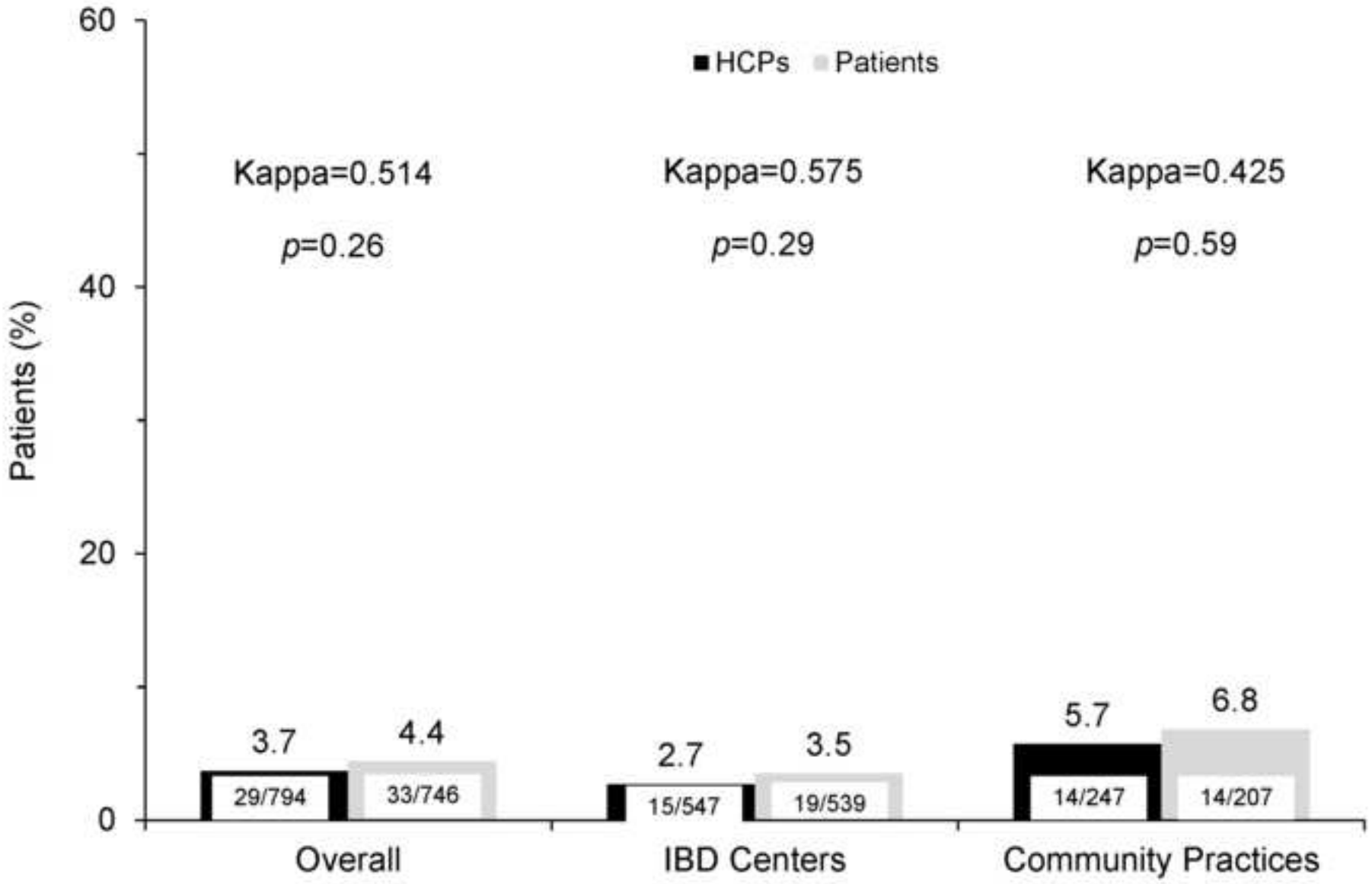

Figure 1C

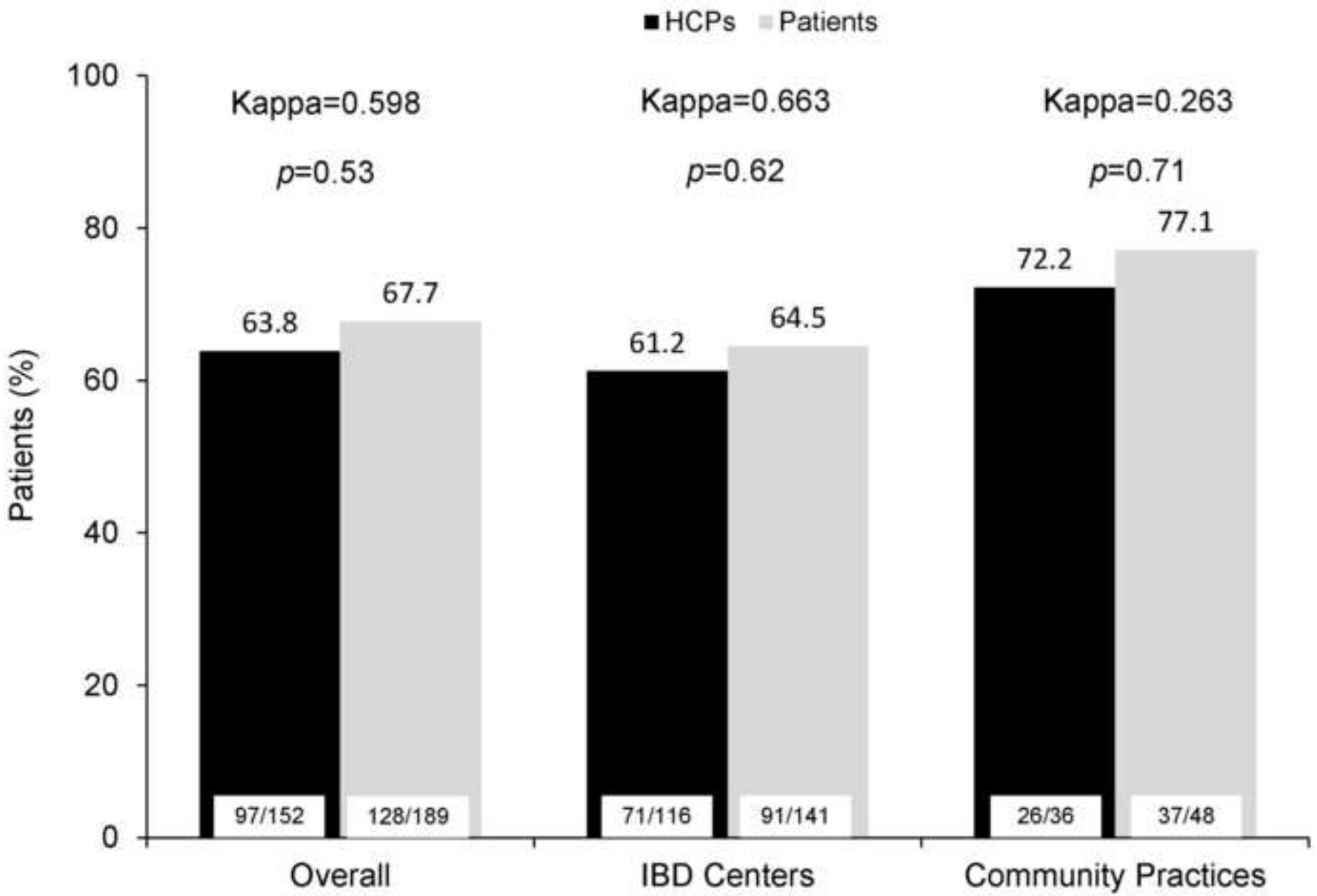

Figure 1D

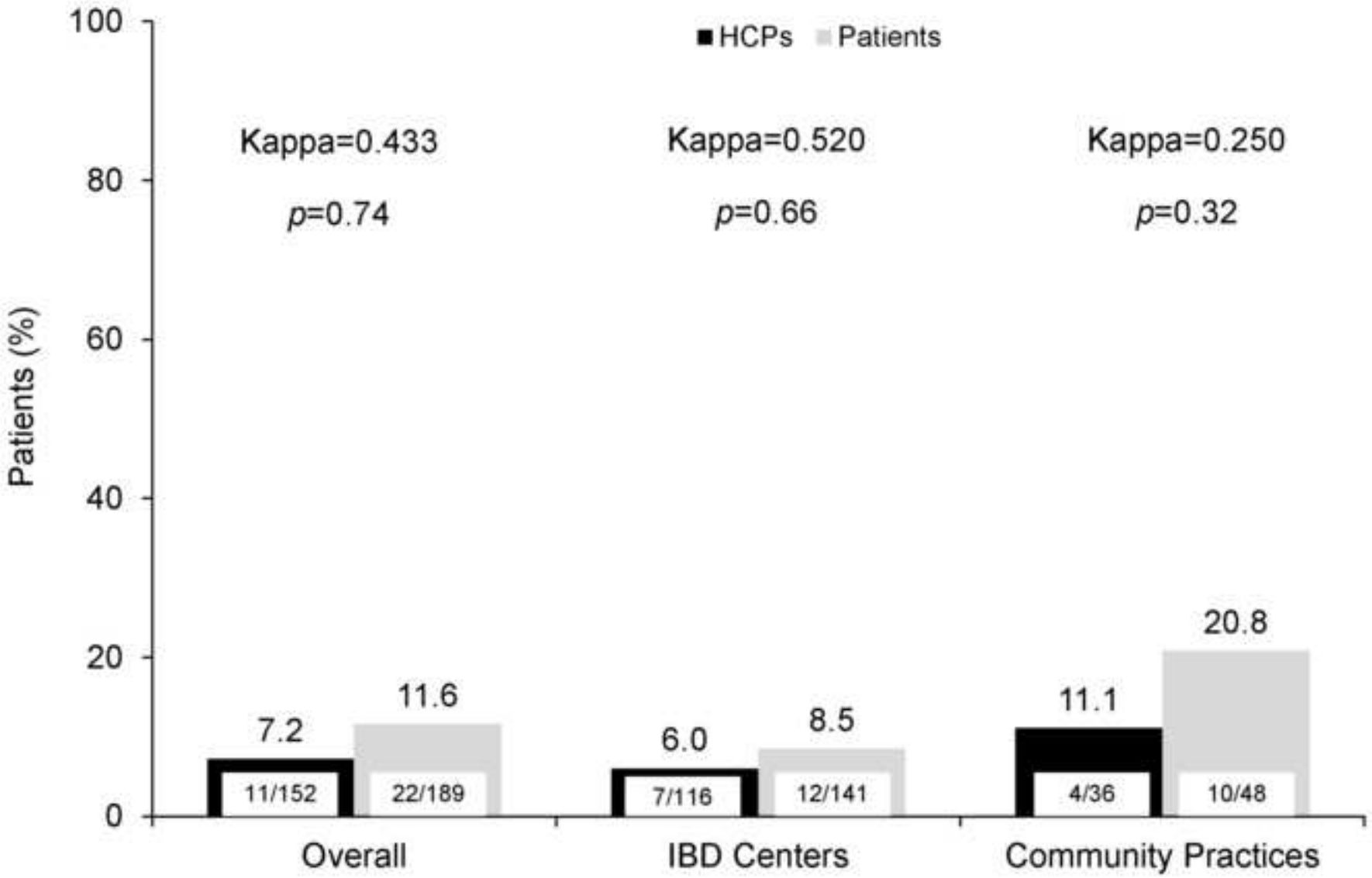

Figure 2

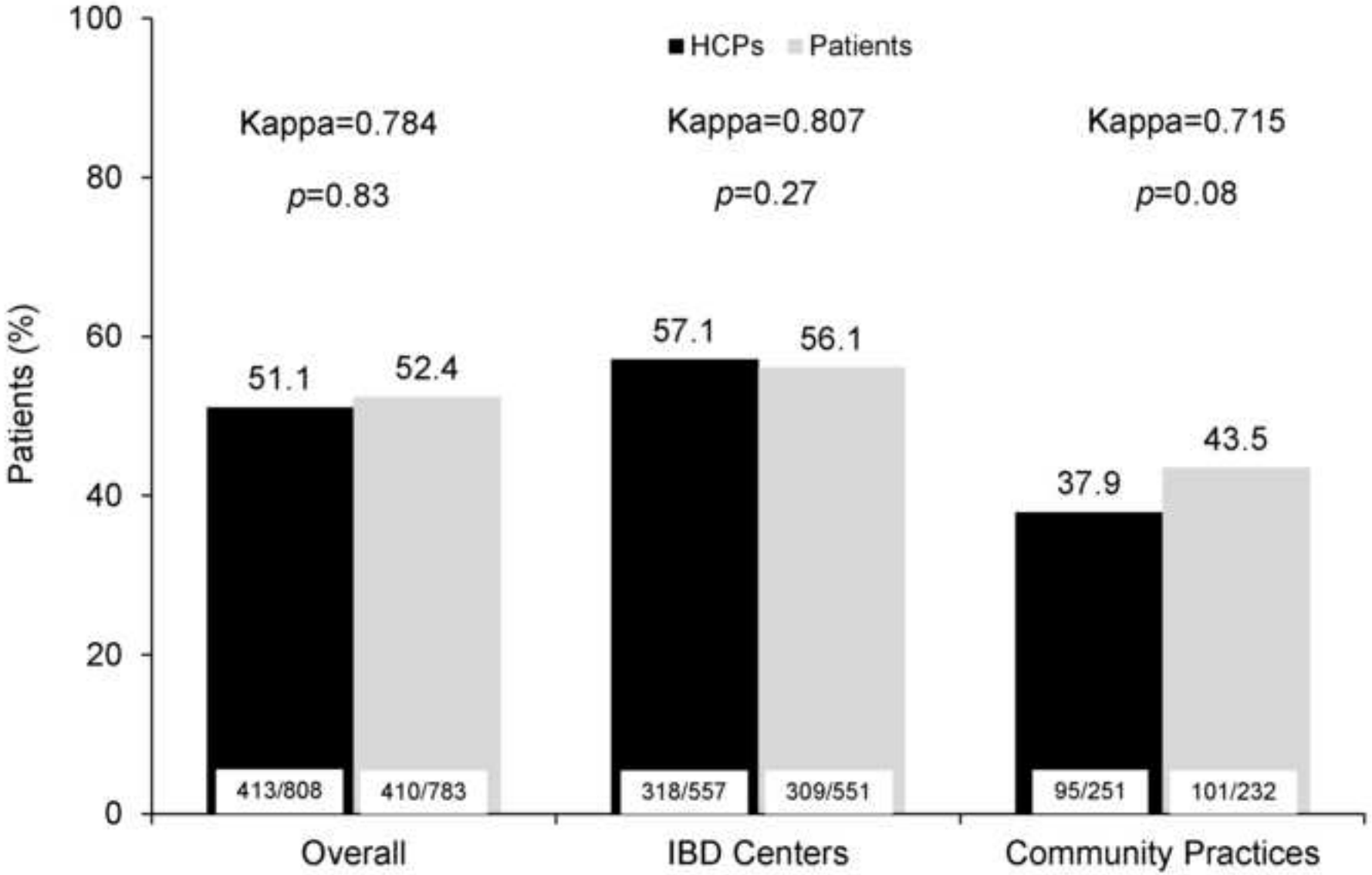

Figure 3

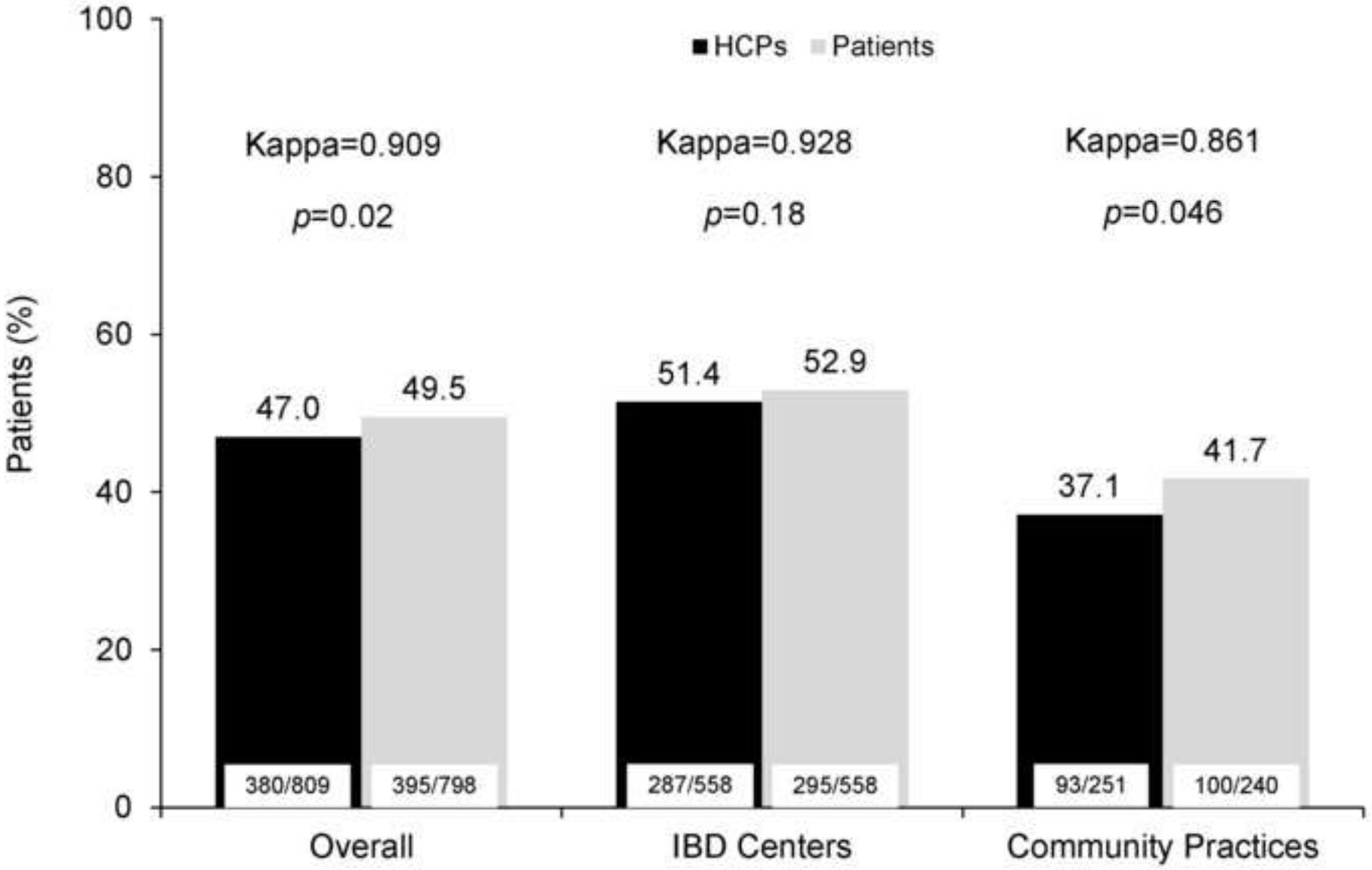

Figure 4